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SUBACUTE DEGENERATION OF THE BRAIN IN PERNICIOUS ANEMIA*

RAYMOND D. ADAMS, M.D.,† AND CHARLES S. KUBIK, M.D.‡

BOSTON

PERNICIOUS anemia is a complicated disease that is characterized by certain changes in the blood and blood-forming organs, in the gastrointestinal tract and in the central nervous system. The primary fault is thought to be an atrophy of the gastric mucosa that induces a deficiency of certain substances essential for the maturation of red cells. The cause of the nerve-fiber degeneration is more obscure, but it has been suggested that deficiency of another factor may account for it. The most important pathologic findings are hyperplasia of the bone marrow, consisting chiefly of the less mature elements of the red-cell series, atrophy of the lingual and gastric mucosa, a variable amount of hemosiderosis in the spleen, liver and kidneys and, in many cases, degeneration of spinal white matter, especially in the posterior and lateral columns. Less well known, and in fact not even mentioned in many textbooks on neurology, are the lesions in the cerebral white matter. Because of this we feel justified in reporting the following observations in 2 cases.

Only within comparatively modern times have the neurologic aspects of pernicious anemia been fully appreciated. Although Lichtheim[1] in 1886 was the first to describe the spinal-cord pathology, Russell, Batten and Collier[2] in 1900 were the first to publish a full clinical and pathological description of subacute combined degeneration.

In the early part of the nineteenth century there were several references to the brain lesions of pernicious anemia in the papers of Wohlwill,[3] Ransohoff,[4] Braun,[5] Schröder[6] and others, but most of them were concerned with findings of dubious significance, such as petechial hemorrhages and changes in cerebral blood vessels. Preobrajensky[7] in 1902 was one of the first to mention degeneration of cerebral white matter, but the abstract of his paper contains such meager clinical and pathological data that the diagnoses of pernicious anemia may be questioned.

Lube[8] in 1913 described cases of pernicious anemia in which he found miliary foci of myelin degeneration in the cerebral white matter. The lesions were said to be globular or oblong, 80 to 100 microns in diameter and closely related to blood vessels.

Barrett[9] in 1913 reported the pathological findings in 6 psychotic patients dying of what was thought to be pernicious anemia, although in most of these cases there were not sufficient data to establish the diagnosis — according to present-day standards. Unfortunately, his material was not well adapted to clinicopathological correlation, because many of these patients had been admitted to the psychiatric ward with obvious depressions or paranoid schizophrenia long before the onset of their terminal illness. In most of them confusion and disorientation developed after the onset of the anemia. On post-mortem examination there was degeneration in the cerebral white matter in only 1 of the 6 cases; in the other 5 cases only an alteration of cortical nerve cells was thought to be present.

Pfeiffer[10] in 1915 reported an unquestionable case of pernicious anemia in which mental symptoms, consisting of drowsiness, inattentiveness, confusion and disorientation, were outspoken features. Post-mortem examination disclosed, in addition to slight alteration of cortical nerve cells, degeneration of the medullated nerve fibers in the white matter of the frontal lobes.

Woltman[11] in 1918 reported 7 cases in all of which there were lesions in the cerebral white matter similar to those described by Lube, Barrett and Pfeiffer. His paper contains the largest series and the most complete description of the brain lesions.

Since then, although clinicians have continued to show an interest in the psychiatric aspects of this disease, as indicated by the publication of many clinical studies, the neuropathology has been neglected. Only a few scattered case reports, including those by Lurie[12] in 1919, Weimann[13] in 1924 and Lebensart[14] in 1934, have appeared in recent

*From the Neurological Unit, Boston City Hospital, the Department of Neurology, Massachusetts General Hospital, and the Department of Nervous and Mental Diseases, Harvard Medical School.

†Instructor in neurology, Harvard Medical School; lecturer in neurology, Tufts College Medical School; neuropathologist and assistant visiting neurologist, Boston City Hospital.

‡Instructor in neurology, Harvard Medical School; neuropathologist and associate neurologist, Massachusetts General Hospital.

years, and in these no attempt was made to relate the mental symptoms to the brain pathology.

Case Reports

Case 1. A 54-year-old Italian woman was in good health until approximately 6 months before admission in August, 1941, to the Boston City Hospital. At first she began to tire easily and complained of paresthesia, first in the feet and legs and a few weeks later, in the hands and arms. The legs gradually became weak and finally, shortly before entry, she could not walk. She lost control of her bladder and bowels. Admission was precipitated by the acute onset of pleuritic pain, cough and fever. The patient was said to have acted queerly for the last several weeks, but it was impossible to obtain a clear account of the mental symptoms from her relatives.

On admission, the temperature was 103°F., the pulse 90, the respirations 28, and the blood pressure 130/80. The patient appeared to be in a fairly well-nourished condition. The skin and mucous membranes were pale. She was drowsy and inattentive, making no effort to respond to many of the questions asked and answering others in monosyllables. So far as could be ascertained she was not melancholic but rather apathetic. When pressed on any point, such as details of history, she became decidedly irritable. Memory for recent events was poor. She was oriented as to place and person but gave the year as 1928. The ocular movements and pupillary reflexes were normal. The tongue was red and smooth and came out in the midline without tremor. The arms could be moved but were very weak, and the legs were almost completely paralyzed. There was no atrophy of muscles. The patient was incontinent of urine and feces. Tendon reflexes could barely be elicited in the arms and were absent in the legs. The plantar reflexes were extensor in type and abdominal reflexes were absent. All forms of sensation were reduced in the arms and almost entirely absent in the legs. The only other physical findings were dullness of the chest on percussion, bronchial breath sounds and a friction rub over the base of the right lung.

The hemoglobin was 62 per cent, and the red-cell count 1,000,000. The white-cell count was 6000, with 2 per cent reticulocytes. The hematocrit was 26.9 per cent, the mean corpuscular volume 139 cubic microns, and the mean corpuscular hemoglobin content 35.9 per cent. Poikilocytosis and anisocytosis were observed in a blood smear. The icteric index was 5.0. Examination of the cerebrospinal fluid showed normal pressure and no cells. The total protein was 38 mg. per 100 cc. The gold-sol curve was 1221000000. Wassermann and Davies Hinton tests were negative. Gastric analysis showed no free hydrochloride. X-ray examination of the chest showed consolidation of the hilar portions of both lungs.

Concentrated liver extract was given parenterally in doses of 10 cc. each day for 7 successive days. Sulfathiazole was administered because of the lung findings and fever. On the 4th hospital day the reticulocytes in the blood rose to 14 per cent and on the 6th day to 22 per cent. The patient remained in a stuporous condition for several days and was only beginning to appear more alert on the 8th hospital day when she suddenly died.

The anatomical diagnoses were pernicious anemia with subacute degeneration of the spinal cord and brain, pulmonary embolus and femoral phlebothrombosis.

Case 2. A 53-year-old Italian woman was admitted to the Massachusetts General Hospital on July 15, 1941. She had had paresthesias in the legs and hands for 2 years. During the 3 months prior to admission there was progressive loss of strength in the legs and finally inability to walk. There had been precipitancy of urination and occasional incontinence. A few days before entry to the hospital she developed pain in the left flank and burning and frequency of urination. There were no remarks in the record concerning the mental status of the patient, but when admitted to another hospital a short time before, it was noted that she was vague as to details of her illness, irritable and difficult to manage. She left against the advice of the physician before a diagnosis could be made.

On admission, the temperature was 99°F., the pulse 90, the respirations 20, and the blood pressure 95/65. The patient appeared to be in a fair state of nutrition. The skin and mucous membranes were pale. Because of marked language difficulty details of mental status were not obtained. On one occasion restraint was necessary. The arm and trunk muscles were weak, and the legs were almost completely paralyzed. There was no muscular atrophy. Vibratory and position sense in the legs were absent. Tendon reflexes were absent in the legs and the plantar reflexes were extensor in type. There was incontinence of feces and urine.

The hemoglobin was 70 per cent. The red-cell count was 2,500,000 with 4 per cent reticulocytes. There was no free

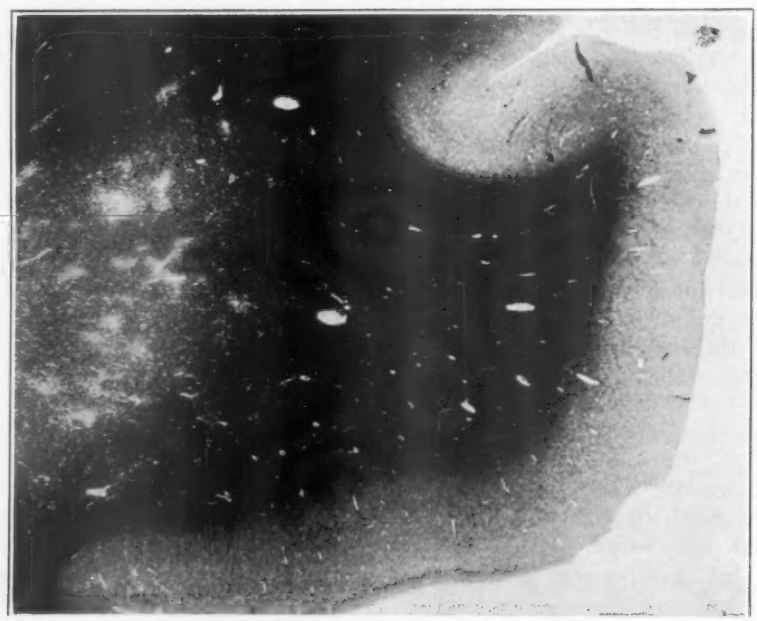

Figure 1. *Diffuse, Uneven Degeneration of White Matter in a Precentral Convolution (Case 2: Spielmeyer stain).*

acid in the fasting gastric contents or after injection of histamine. The cerebrospinal fluid showed normal pressure. The total protein was 37 mg. per 100 cc., and the Wassermann reaction was negative. The urine gave a + test for albumin, and contained many white-blood cells.

The patient developed fever, tachypnea and signs of pulmonary consolidation. Following five injections of concentrated liver extract the reticulocyte count rose to 8 per cent on the 5th hospital day. Death occurred suddenly on the 8th day.

The anatomical diagnoses were pernicious anemia with subacute degeneration of the spinal cord and brain, pulmonary embolus and acute pyelonephritis.

FIGURE 2. *Degeneration of White Matter in the Right Occipital Lobe (Case 1: Weigert stain).*

MORBID ANATOMY

The pathological findings were so nearly alike in these 2 cases that the following description applies equally to both.

Gross Findings

Gross changes in the central nervous system were relatively inconspicuous. There was no atrophy of cerebral convolutions or enlargement of the ventricles. The leptomeninges were transparent, and the large cerebral arteries were not especially atherosclerotic. In Case 1 (after fixation in formalin) there were innumerable minute gray foci on the cut surface of the white matter, which gave it a mottled appearance. These were approximately 1 mm. in diameter and were disseminated through all parts of the centrum and corpus callosum and, to a slight degree, the convolutional white matter. No such gross changes were observed in Case 2.

On the cut surface of the spinal cord in both cases the white matter in the posterior and lateral and to a lesser extent the ventral columns was gray and translucent. These changes were most marked in the thoracic and cervical portions.

Microscopic Findings

Cerebrum. Lesions were found in the central and convolutional white matter of the cerebral hemispheres, the cerebellar peduncles and, in Case 2, the optic tracts near the chiasm. The characteristic changes in the cerebrum were best demonstrated in sections stained for myelin. In these preparations the affected white matter was diffusely but unevenly pale, the unevenness being due to a more pronounced degeneration in some regions, usually around blood vessels (Figs. 1, 2, 3, 4 and 5). In many such foci, varying in size from 50 to 150 microns the myelin was completely degenerated. The axis cylinders as well as myelin sheaths were affected, though possibly not to the same extent. In the perivascular zones of more severe degeneration there were numerous macrophages filled with fat (Fig. 6). The astrocytes and oligodendrocytes were increased in number throughout the white matter, but more so just beneath the cortical gray matter than in the deeper white matter, where the myelin was more severely degenerated. The astrocytes had large cell bodies and cytoplasmic processes that were distinctly stained in Nissl preparations. The nerve cells in the cerebral cortex were not remarkable. There were no swollen cells with eccentric nuclei and chromatolysis, such as are commonly observed in pellagra and some other vitamin-deficiency diseases.

FIGURE 3. *Degeneration in Internal Capsule and Corpus Callosum (Case 2: Weigert stain).*

Cerebellum. The Purkinje cells appeared to be normal. There were no foci of nerve fiber degeneration.

Spinal cord. The findings in both cases were identical. There was degeneration in the greater part

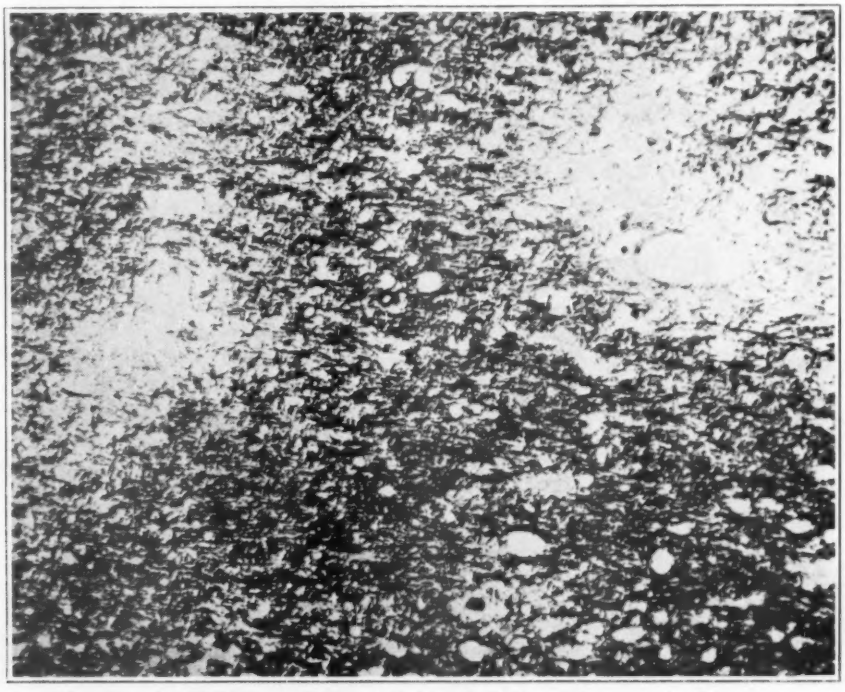

FIGURE 4. *High-Power View of the Myelin Degeneration Seen in Figure 1. Note the relation of the lesions to blood vessels.*

Brain stem. Nerve-fiber degeneration like that in the cerebral white matter was observed in the middle cerebellar peduncles. The midbrain and medulla were normal.

of the white matter except for a narrow zone next to the central gray matter. The posterior, postero-

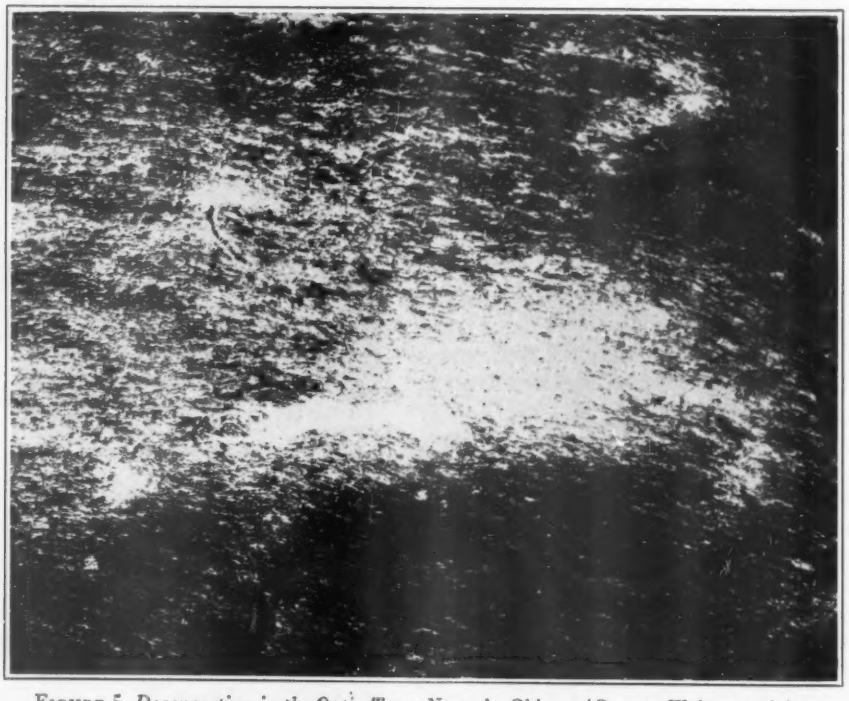

FIGURE 5. *Degeneration in the Optic Tract Near the Chiasm (Case 1: Weigert stain).*

lateral and at some levels anteromedial columns were most severely affected (Fig. 7). Axis cylin-

ders as well as the myelin sheaths were destroyed. There was an unevenness similar to that of the brain lesions, which was more conspicuous in longitudinal than in cross sections (Fig. 8). The areas of more pronounced degeneration seemed to have no relation to blood vessels. Fat-filled macrophages were abundant. There was singularly little reaction of astrocytes, although they had increased somewhat in size and possibly in number. Nerve cells in the spinal cord were not remarkable.

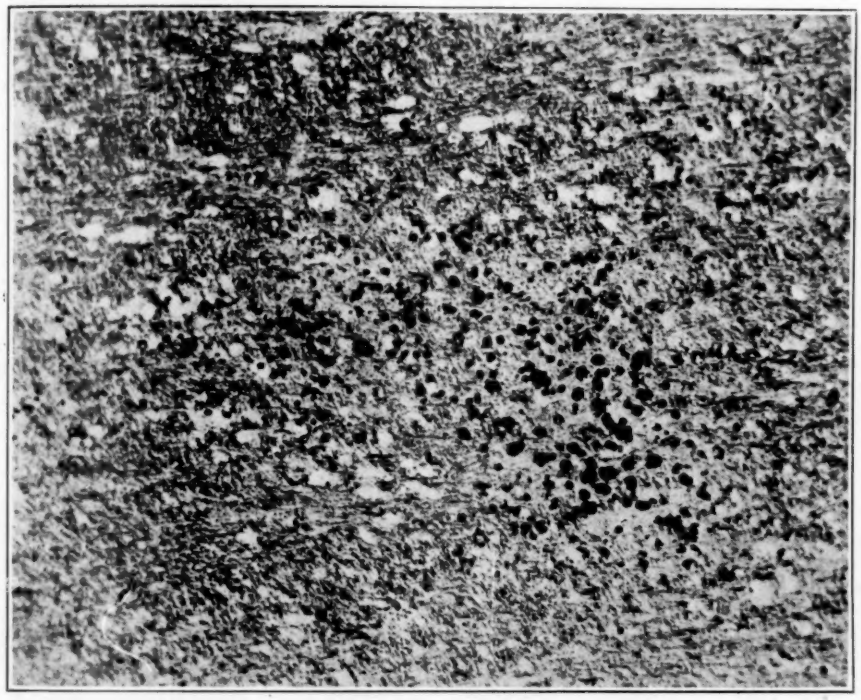

FIGURE 6. *An Area of Nerve-Fiber Degeneration (Case 1: fat stain).*
The fat in the macrophages corresponds to the distribution of the myelin degeneration.

DISCUSSION

Subacute Degeneration of Brain

The findings in these cases confirm the observations of others that cerebral lesions may occur in pernicious anemia. Furthermore, the cerebral and spinal-cord lesions are almost exactly alike. In both, the essential pathology consists of a more or less diffuse though uneven degeneration of the white matter, with little or no proliferation of fibrous glia. Because of this similarity it seems reasonable to suppose that this degeneration of cerebral white matter is as specifically related to pernicious anemia as is subacute combined degeneration of the spinal cord.

These changes are unique and quite unlike those that occur in cerebrovascular disorders, multiple sclerosis, Schilder's diffuse periaxial encephalitis and other more chronic degenerative diseases. Nor, in our experience, do they resemble the findings observed in pellagra or the central neuritis of Meyer.[15] In our cases of pellagra the columns of Goll were degenerated throughout their course as in secondary degeneration from a dorsal-root lesion; this process was not uneven as in pernicious anemia and was accompanied by a pronounced gliosis. No degeneration of cerebral white matter was observed. Moreover, there were swelling and central chromatolysis of the anterior-horn cells and of the larger pyramidal cells of the cerebral cortex, whereas nothing remotely resembling this was found in our cases of pernicious anemia. Although it is true that degeneration of the corticospinal tracts in pellagra has been reported by others, this too may be secondary to destruction of Betz cells in the motor cortex.

Certain authors have reported small hemorrhages and nerve-cell changes in the brain in pernicious anemia. Small, recent perivascular or capillary hemorrhages so often occur as a terminal event in many diseases that they are not of any great significance. The matter of nerve-cell changes is more difficult to assess. In some papers the descriptions are too ambiguous to permit accurate interpretation, whereas in others nonspecific changes, such as shrinkage and pigmentary atrophy, have been assigned undue importance. Where nerve-cell swelling and central chromatolysis like that of pellagra were present (Barrett,[9] Pfeiffer[10] and

Woltman[11]), the possibility of associated factors such as malnutrition and vitamin B deficiency cannot be dismissed.

Relation of Subacute Degeneration of Brain to Subacute Combined Degeneration of Spinal Cord and to Pernicious Anemia

Just as degeneration of the posterior columns seems to be the initial event in subacute combined degeneration, so do spinal-cord changes usually, if not invariably, precede the brain changes. Clark[16] and Greenfield and O'Flynn[17] have shown that the posterior columns are first affected, and that when both lateral and posterior columns are involved the oldest lesions are in the latter. In this connection, many cases have been described in which there were spinal-cord lesions without brain lesions, but in all authentic reports of subacute degeneration of the brain there have been spinal-cord lesions. Thus it seems that the order of involvement of the central nervous system is posterior columns, then lateral and anterior columns and finally cerebral white matter.

That pernicious anemia, with or without subacute combined degeneration, may develop as a consequence of carcinoma of the stomach or of gastric resection is suggested by a few carefully studied cases. Similarly, Bertrand and Ferraro[18] have reported a case of gastric carcinoma with macrocytic anemia and brain and spinal-cord lesions exactly like those in our cases. In cases such as these it is obviously possible that the gastric condition bears no causal relation to pernicious anemia or subacute degeneration.

Relation between Brain Lesions and Mental Symptoms

It is a well-known fact that patients with subacute combined degeneration often exhibit mental symptoms that vary from slight irritability and suspiciousness to a marked confusional psychosis. The question naturally arises as to the relation between these symptoms and the pathologic changes observed in the brain. Some writers, notably Pfeiffer,[10] Barrett[9] and Lurie,[12] affirm a causal relation, whereas Woltman[11] concludes that well-marked psychoses have little or nothing to do with the destroyed areas. In reviewing Woltman's case material, however, one finds mental symptoms such as irritability, mental sluggishness, fluctuation in attention and delirium in all the cases in which the mental status was recorded (Table 1).

The observation of degeneration in the optic tracts provides an explanation for reports of impaired vision by Cohen,[19] Turner[20] and others. In our case the record gives no information concerning vision. Bickel[21] has also reported foci of degeneration in the optic nerves of a patient with subacute combined degeneration of the spinal

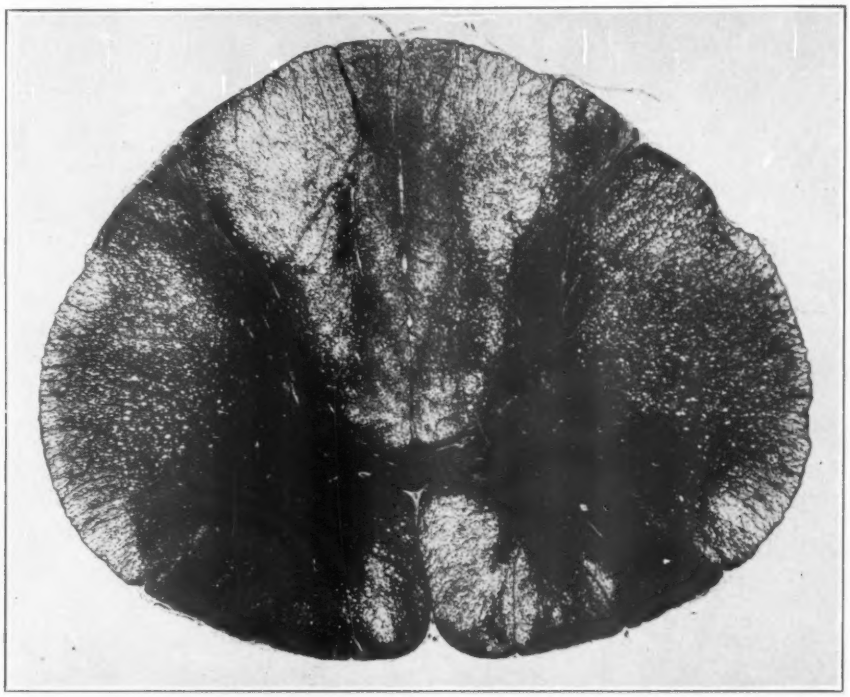

FIGURE 7. *Subacute Combined Degeneration (Weigert stain).*
There is an uneven degeneration of spinal white matter in the posterior, lateral and anterior columns. Note the cribriform appearance and the relative symmetry of the lesions.

TABLE 1. *Summary of Pertinent Data on Patients with Pernicious Anemia.*

CASE NO.	AGE	SEX	RED-CELL COUNT	HEMOGLOBIN	COLOR INDEX	ACHLORHYDRIA	SYMPTOMS AND SIGNS		PATHOLOGY	
							SPINAL CORD	BRAIN	SPINAL CORD	BRAIN
	yr.		$\times 10^6$	%						
1 (Pfeiffer[10])	55	M	0.9	30	—	?	Paresthesia, weakness of legs, sensory loss and ataxia	Drowsy and confused	Degeneration of posterior and lateral columns	Foci of myelin degeneration in cerebrum
2 (Lurie[12])	75	F	—	30	1.7	?	Paresthesia, weakness of legs, absent tendon refloxes and Babinski sign absent	Irritable, deluded and confused; hallucinations (auditory); semicomatose.	Degeneration of posterior columns	Foci of nerve-fiber degeneration in cerebral white matter
3 (Lurie[12])	54	F	—	10	—	?	Paresthesia and ataxia, absent tendon jerks and Babinski sign	Irritable and excitable, then drowsy and irrational; faulty memory.	Degeneration of posterior and lateral columns	Focal necrosis in medulla, pons and cerebrum
4 (Barrett[9])	47	M	1.5	45	—	?	Not stated	Suspicious and melancholy for 9 yr.; more recently auditory hallucinations, poor retentive memory and confabulation.	Degeneration of posterior and lateral columns	Focal degeneration of nerve fibers in cerebrum with proliferation of macrophages
5 (Woltman[11])	51	M	?	?	?	?	Aching legs, girdle sensations, weakness of legs, absent tendon jerks and Babinski sign (early)	Unreasonable, irritable and stupid (late)	Degeneration of posterior, lateral and anterior columns	Myelin degeneration in cerebral white matter, medulla and cerebellum
6 (Woltman[11])	42	M	1.7	47	—	?	Paresthesia, increased tendon jerks, Babinski sign and diminished sensation	Mental sluggishness and delirium	Not examined	Perivascular degeneration of nerve fibers in cerebrum
7 (Woltman[11])	40	F	?	?	?	?	Paresthesia, weakness of legs and lively tendon reflexes	Questionable mental status	?	Diffuse and focal nerve-fiber degeneration in cerebrum
8 (Woltman[11])	48	M	1.0	18	—	?	Impaired sensation; Romberg sign.	Marked fluctuation in attention	?	Scattered areas of myelin degeneration in cerebrum
9 (Woltman[11])	51	M	2.0	50	—	?	Paresthesia, ataxia and impaired sensation; Babinski sign.	Inattentive, faulty memory, depressed mood and logical thinking disordered	Degeneration of posterior and lateral columns	Degeneration of nerve fibers in occipital lobes
10 (Woltman[11])	42	M	0.8	18	—	?	?	Delirious, talkative and restless	?	Degeneration of nerve fibers in focal areas of cerebral white matter
11 (Weimann[13])	55	F	—	37	1.3	+	Paresthesia, incontinent sphincters, ataxia and spasticity	Defective memory, ideas of persecution, disoriented and demented	Posterolateral sclerosis	Focal lesions in cerebral white matter and diffuse gliosis
12 (Lebensart[14])	45	M	—	65	1.2	+	Paresthesia, weakness, ataxia, sensory loss and plantar reflexes	Stuporous and drowsy	?	Status spongiosus in cerebral white matter with proliferation of macrophages
13 (Adams and Kubik — Case 1)	54	F	—	50	—	+	Paresthesia, weakness, incontinence, loss of reflexes, impaired sensation and Babinski sign	Confused, disoriented, poor memory and stuporous; semicomatose.	Degeneration of posterior, lateral and anterior columns	Focal and diffuse degeneration of nerve fibers in cerebral white matter, corpus callosum, cerebral peduncles and brain stem
14 (Adams and Kubik — Case 2)	53	F	2.5	70	—	+	Paresthesia, weakness, incontinence, loss of tendon reflexes and Babinski sign; some sensory loss.	Irritable and unreasonable; restraint because of mental confusion.	Degeneration of posterior, lateral and anterior columns	Uneven degeneration of nerve fibers in cerebral white matter, optic chiasm and cerebellar peduncles

cord. In his case there were bilateral central scotomas and optic atrophy.

On the basis of these observations we favor the supposition that both subacute combined degeneration of the spinal cord and subacute degeneration of the brain represent an advanced stage in a specific process that is induced by a deficiency of certain substances necessary to the metabolism of myelinated nerve fibers. It is not to be expected that every patient with pernicious anemia will have demonstrable brain lesions, but all those in whom there are definite and widely disseminated brain lesions will probably have mental disorders.

An analysis of our cases and others indicates that patients with brain lesions have mental symptoms. The converse is not necessarily true, since cerebral lesions are not always found in cases in which mental symptoms have been present.

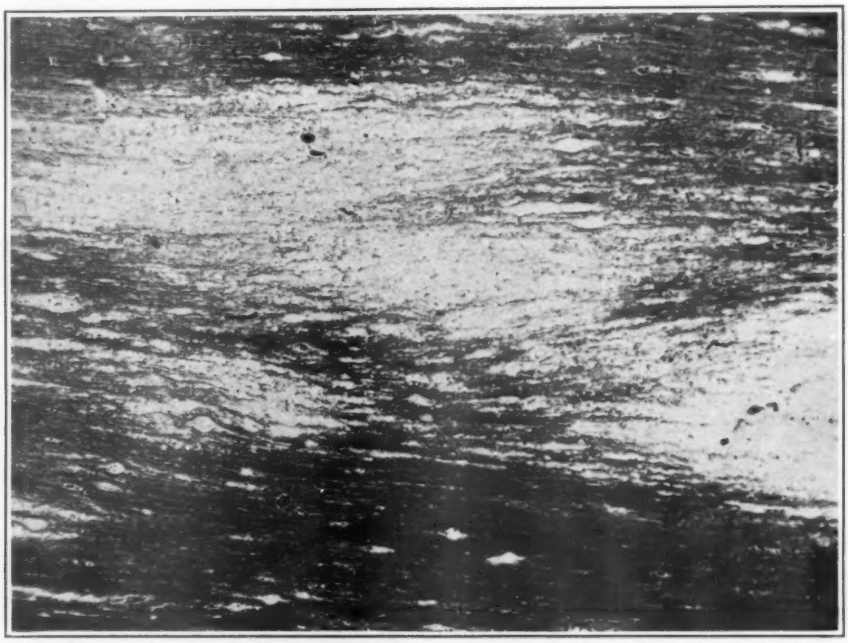

FIGURE 8. *Degeneration of Myelinated Fibers in a Lateral Column of the Spinal Cord (Case 2: Spielmeyer stain).*
Note the resemblance between the cord lesions and the brain lesions.

SUMMARY

The clinical and pathological findings in 2 cases of pernicious anemia with subacute degeneration of the brain and spinal cord are described. In each, there were well-marked neurologic and psychiatric symptoms.

The important pathologic changes consisted of a diffuse uneven degeneration of nerve fibers in the spinal cord and cerebral white matter, with relatively little proliferation of fibrous glia. The brain lesions resembled the cord lesions so closely that there could be little doubt concerning their identity.

The pathologic process is unique and easily distinguished from that of other diseases involving the cerebral white matter and from that of pellagra.

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PART-TIME PROTECTIVE ENVIRONMENT AND WORKING PAROLE AS AN ADJUVANT IN THE TREATMENT OF ALCOHOLISM

JOSEPH THIMANN, M.D.*

BOSTON

ASIDE from other considerations, — physiologic, psychologic and sociologic, — the extremely high cost to cities, states and the federal government of the care of alcoholic patients who become a public liability has been noted so often by writers on the subject that it would be duplication to quote them at length here. The seriousness of the problem from the economic viewpoint, however, is summed up in the following statement from a paper read by Dr. Merrill Moore at the fifty-first annual meeting of the Association of Life Insurance Medical Directors of America (October 17 and 18, 1940), entitled "Alcoholism: A public health problem":

> Its [alcoholism's] cost to the individual, the family and the community cannot be expressed in simple figures, for it involves such intangible and remote costs as the tax rate on your real property, the amount of money available in a tax dollar for schools and roads and the dividends which certain of your well-invested securities yield. When one reckons the cost of caring for chronic alcoholics in jails and for acute alcoholics in hospitals, the resulting figure represents only the surface cost. Persons with alcoholic psychoses increase the budget of the Massachusetts State Department of Mental Health by 10 per cent; broken homes resulting from alcoholism cause municipal and federal budgets for relief to be greatly increased; the costs incident to accidental deaths which are indirectly due to the intemperate use of alcohol are tremendous.

This is looking at the problem from the negative side. When one attempts to deal with it in a positive way, he must answer the questions, "How can this economic waste be prevented?" and "How can an alcoholic patient be helped toward physical, emotional and economic rehabilitation?" A plan that has been worked out at the Washingtonian Hospital, although it may not answer these questions fully and finally, at least seems to be a signpost indicating the way.

This is a system of working patients; that is, the patient, while still under treatment, returns to his former occupation (or finds a new job), but spends all his free time at the hospital. This arrangement has a number of advantages. The patient is in a protected environment during his free time. His evenings and nights are spent at the hospital if he is working in the daytime or his daytime hours if he is working at night, and he is under the shelter of the hospital over week ends, a time difficult to bridge if he is living outside because of the temptation to seek the conviviality of a tavern in his loneliness and because he has nothing to do. He is, moreover, removed from the emotional instability of a home environment in which the wife or mother may have little understanding of his problem, and from the company of drinking companions. He is put on his feet financially, so that he can pay, or at least contribute to, his hospital fee and the charge for special treatment, such as the conditioned-reflex therapy. He becomes, while still under treatment, gradually more self-reliant and responsible, and self-respecting. He is in daily contact with the physician, so that psychotherapeutic interviews may help him over difficult periods.

Under this arrangement, patients whose maladjustment to life caused an acute intoxication every few weeks, with resulting inability to hold a job and be self-supporting, have worked daily and efficiently without recourse to alcohol. In some cases this has been so even before the conditioned-reflex treatment was given or psychotherapy could be expected to bear results. The patients were rid of the vicious cycle of relapses, which caused despondency and lack of faith that they would ever be abstinent, which, in turn, led again to drinking. On working parole they have gained self-confidence and self-assurance from the realization that they are being abstinent and are economically successful. Thus they grow increasingly better able to adjust to the difficulties of life, to face reality and to become poised and happy people.

CASE 1. A. B., a 38-year-old Nova Scotian, who worked as a painter in a local shipyard, was admitted to the hospital in December, 1942. He was deeply intoxicated on admission, having been drinking continuously for 3 days. According to his story, he had his first drink at the age of 18 and drinking became a problem when he was 28. At the time he entered the hospital, he was drinking a quart of whisky daily and some beer and his longest period of sobriety had been 4 months. He gave as the cause of his drinking marital difficulties.

The hospital social worker was requested to interview the patient's sister and to secure a complete social history, which, in abstract, was as follows: The patient's parents were

*Medical director, Washingtonian Hospital.

natives of Nova Scotia. His father was a strict disciplinarian, a dominant person and definitely the head of the household. His mother was a mild woman, gentle and sympathetic, and there was a close tie between the patient and her. The patient was always especially interested in the mature, aggressive, masculine type of girl who is fond of sports. At the age of 26 he married a girl who was, according to the patient's sister, an aggressive, irresponsible person. There were three children by the marriage. Almost from the beginning there was much incompatibility between the patient and his wife, and after 7 years they separated. Later they became reconciled, but 4 years after the first separation they again separated and the patient went to live with his sister. Throughout the years of his marital difficulties, the patient turned frequently for help to his two sisters, who were described as fine, intelligent women with high standards but rather moralistic, repressive and critical in their attitudes.

After he had been in the hospital for 2 weeks, the patient expressed a desire to take the conditioned-reflex treatment, which was begun on December 28. The preliminary series of treatments was finished on January 5, 1943. With the assistance of the social worker, arrangements were made for the patient to return to his former place of employment on January 11. It was explained to the employer that he had come voluntarily to the Washingtonian Hospital and had been co-operative in treatment plans, and, as he had always been a good worker, his employer was willing to rehire him.

The patient was advised to live at the hospital. He was given a low rate for his board, and after he began working he assumed this obligation himself.

From February 7 until July 12, the patient had four reinforcements of the conditioning treatment. During this period, also, he was in close contact with the medical director of the hospital, the hospital social worker and the social worker at the referring agency. He earned sufficient pay to meet his hospital bills, contribute to the care of his children and pay the first installment on his income tax.

On August 16, the patient injured his ankle while at work and was transferred to a general hospital. Because this injury made climbing stairs inadvisable he could not return to the Washingtonian Hospital. He was, however, persuaded to come in for week-end stays and to make short visits to the physician during the week. He has now been totally abstinent for eighteen months.

CASE 2. C. D., a 43-year-old American citizen of Canadian birth, began drinking at the age of 17 and had never been abstinent since then. Drinking became a problem 4 years before entrance to the hospital, when he realized that he was unable to stop and that this habit was interfering with his work. He was referred to the hospital by the Court that found him guilty of drunkenness. There had been innumerable arrests for the same offense, and he had been confined at the Bridgewater State Farm six times. When drunk he was belligerent and dangerous.

According to the social history, the patient's mother had "lived for her children" and was resentful when her sons married and left her. She had been especially fond of the patient and had given him privileges that his brothers did not share. His father, on the other hand, was a severe disciplinarian and "overreligious." The patient had to leave school to go to work at the age of 13 and obtained a job as an apprentice shipwright in a local shipyard. He was a good worker and later got a job as a wood caulker, first class, at the Charlestown Navy Yard. He held this job for 5 years and then secured work at the Brooklyn Navy Yard, where he worked for 3 years. At the end of that time he returned to Boston, was re-employed at the Charlestown Navy Yard and continued to work there for 4 years. At that time his jail record commenced, and since 1939 the patient had not worked.

Meanwhile, at the age of 21, he had married a girl several years his junior. This marriage was not a happy one from the beginning, and the couple separated within a year. At the age of 26 the patient married for the second time. This wife was 9 years older than he, had been previously married and had five children. There seems to have been a strong mother-son relation in this marriage, and the patient "relied and leaned on" his wife. There were four children by this marriage.

The patient was brought into the hospital by a court probation officer on February 16, 1943. He was shabby and unkempt, stated repeatedly that he had dragged his wife and children down to the dregs and they would be better off without him, and seemed apprehensive about being hospitalized. He was, however, anxious to have help, since he was afraid he would again be sent to Bridgewater. He was admitted for a 2-week period of observation. At the end of that time, it was suggested that he return to his job on working parole and save money to pay for the conditioned-reflex treatment. (It is believed that assuming financial responsibility by the patient as early as possible is psychologically constructive.) After working a month under this arrangement, he expressed his amazement that he could pass beer parlors and other places where liquor was sold without being tempted to go in and have a drink. He worked out a budget with the social worker and began to save toward his conditioning treatment.

On May 3, the preliminary series of treatments was begun, and to date the patient has had four preventive reinforcement conditionings. A plan was worked out whereby he gradually spent more and more of his nights at home. He was given two raises in pay.

In view of the severity of his alcoholism, this patient remained as a boarder at the hospital for a full year. He still gets easily upset over small matters, but he is being exposed gradually to the tensions that he meets outside the hospital, so that he will learn to handle them without drinking. Considering his long period of drinking and his court record, it is extremely gratifying that he continues to be abstinent after a period of 9 months.

CASE 3. A 32-year-old Irish-American had been in the hospital four times previous to his last admission in January, 1943. He began drinking when he was 22 and continued until the age of 25, when he stopped. No clear history could be elicited concerning when he resumed drinking, but his first admission to the hospital was in October, 1937. He came in again in March, 1938, in May, 1942, and in November, 1942. His attitude on each of these admissions was hostile and suspicious, and he stated that drinking was not a problem for him, since he did not drink to excess. On his fifth admission in January, 1943, however, he was more co-operative and the following social history was elicited.

The patient left school after 3 years of high school and went to work for a gasoline concern, with which he stayed for 10 years. Business later became dull and about 3 years previous to admission he got a job retreading tires. His father died when he was 10 years old and his eldest brother, who was 20 years older, seems to have taken the father's place. The patient was his mother's favorite child, and after he married at the age of 23 the mother lived with his wife and himself. His married life was harmonious until 3 or 4 years ago, when his wife's mother came to live with them. Both she and her daughter drank and arguments ensued about this, since the patient did not like to have drinking in the home. He decided that it was right for him to drink if they did, and it was shortly after this that he was admitted to the hospital for the first time. Finally he left home and took a room. Because of loneliness and worry about his child, he continued to drink. Fear that the child might be put in a "home" seemed to bring about a change in his attitude, for on his final admission he was anxious for treatment.

It was arranged that the patient should stay at the hospital on working parole, meeting his board out of his pay and saving money for the conditioned-reflex treatment. To date he has been working regularly and is entirely abstinent.

It has been found that such a protective environment should be continued for about a year, supplemented, as mentioned above, by conditioned-reflex treatment, psychotherapy, social adjustments and, if necessary, relaxation therapy. The resources of this hospital are limited. It is located in a tavern and package-store district; comfortable living quarters and adequate grounds for outdoor activities are lacking; no skillful and enthusiastic recreational therapists are available to schedule and organize the patients' free time in a pleasant way. If, in spite of all these drawbacks, constructive and

encouraging work has been accomplished, how much more could be done under more favorable conditions! With adequate grounds and resources, for instance, workshops might be set up where patients could engage in such work as carpentry, cabinetmaking, soldering and repairing mattresses, for which they would be paid a regular salary. In this way, many patients could be salvaged who had not yet reached a point in their rehabilitation where they could safely be allowed to take employment outside the hospital but would work well and efficiently if adequately safeguarded. Such patients, moreover, could be kept under treatment for an indefinite period of time, meanwhile learning a trade or becoming more adept at their own trade. When finally discharged, they would emerge from the hospital better equipped physically, mentally and economically to carry on.

Such a plan would be far superior to the present practice of sentencing an alcoholic patient to a state farm, where he works under compulsion. In sentencing a man to labor, no attempt is made to win his co-operation through an appeal to the more mature and ethical components of his personality. Such compulsory treatment of a sick person — which an alcoholic patient really is — is likely to elicit feelings of hostility, which prevent any good effects from being achieved. In the plan outlined above, on the other hand, the patient would work on a purely voluntary basis. He would be treated as a mature, intelligent person, capable of co-operating in the plans for his rehabilitation, and his interest in helping himself would be encouraged and developed. This approach is the very keystone of successful treatment, for unless the patient's full co-operation has first been secured, the other steps in the plan of therapy — conditioned-reflex therapy, psychotherapy and social readjustments — cannot be effective.

Summary

The role of a part-time protective environment with working parole (in contrast to full-time confinement) as an adjuvant to conditioned-reflex treatment and psychotherapy is discussed. According to the experience at the Washingtonian Hospital, this threefold plan represents the most promising and well-organized treatment for alcoholic patients.

41 Waltham Street

EPIDEMIC KERATOCONJUNCTIVITIS*

Report of a Case with Marked Systemic Manifestations

JOHN J. CURRY, M.D.,† AND FRANCIS C. LOWELL, M.D.‡

BOSTON

THE clinical features of epidemic keratoconjunctivitis have been well described by Hogan and Crawford[1] and more recently by Sanders and his co-workers.[2] According to these authors, at the onset there was usually unilateral hyperemia and swelling of the palpebral conjunctivas and "a sandy feeling" in the eye. This was associated with lacrimation, but only rarely was there a purulent discharge. After twelve to thirty-six hours the bulbar conjunctiva also became congested and hyperemic. Edema of the lids was often present in varying degrees. In a few cases pseudomembranes appeared, usually on the conjunctiva of the lower lid. Corneal infiltration appeared in 52 per cent of Sanders's series of 80 cases, and in 33 per cent of these was associated with 5 to 15 per cent impairment of vision. In 42 per cent of the series the other eye became involved after varying periods of time. Swelling of the preauricular glands was found in 93 per cent of the cases, and considerable significance was attached to this finding.

Among the systemic manifestations headache was by far the most frequent, appearing in 61 per cent of the cases. As a rule it was moderately severe and not relieved by analgesics. Fever and malaise were also noted.

It appeared that trauma or inflammation might predispose the eye to an attack of epidemic keratoconjunctivitis. The possibility of transmission by means of instruments and solutions used in eye examinations in the New York epidemic was also mentioned.

The sequence of appearance of the objective signs and their intensity varied greatly in the cases studied. The initial symptoms had no bearing on the duration or severity of the disease.

The following case is reported because it had many of the features of epidemic keratoconjunctivitis in association with prominent systemic manifestations. An opportunity was afforded for hospital study, which revealed the presence of abnormal lymphocytes in the blood, with a marked fall in polymorphonuclear cells during convalescence, a palpable spleen and a normal spinal fluid. Antibody for the virus of epidemic keratoconjunctivitis appeared in the serum after recovery.

*From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†Instructor in medicine, Boston University School of Medicine; chief resident, Evans Memorial, Massachusetts Memorial Hospitals.

‡Assistant professor of medicine, Boston University School of Medicine; member of staff, Evans Memorial, Massachusetts Memorial Hospitals.

Case Report

W.M., a 27-year-old, married metal worker, was admitted to the Massachusetts Memorial Hospitals on February 4, 1943, because of severe frontal and occipital headache associated with fever of 5 days' duration. He had previously been well except for a mild respiratory infection that cleared completely 14 days before the onset of the present illness. One week before admission he had a chilly sensation followed by fever, which subsided by evening. Fever recurred the following morning, and at that time he noted swelling about his eyes, which became quite painful. Lacrimation was profuse. The lymph nodes in the region of the ears were enlarged and tender. Frontal and occipital headaches appeared and quickly became severe. Salicylates failed to give relief. With an increase in fever, sulfathiazole was given in therapeutic amounts. This produced no change in the patient's condition, and the drug was discontinued after 3 days.

The red-cell count was 4,500,000 and the hemoglobin 12.5 gm. per 100 cc. The white-cell count was 6800, with 76 per cent neutrophils, 18 per cent lymphocytes, some of which were atypical, 5 per cent monocytes and 1 per cent eosinophils. The urine was normal on several examinations. The Hinton test on the blood serum gave a negative reaction. The blood nonprotein nitrogen was 21 mg. per 100 cc., and the fasting blood sugar 81 mg. The total protein of the blood was 6.09 gm. per 100 cc., with the albumin and globulin fraction 2.63 and 3.46 gm., respectively. Several cultures of the throat, eyes and blood failed to show any pathogenic organisms. Repeated agglutination tests on the blood serum for typhoid, paratyphoid, typhus and undulant fevers and dysentery were negative. The blood sulfathiazole level was zero.

The course in the hospital is shown in Figure 1, in which the major features of the illness are correlated. Shortly after entry the patient was placed in a darkened room and strictly

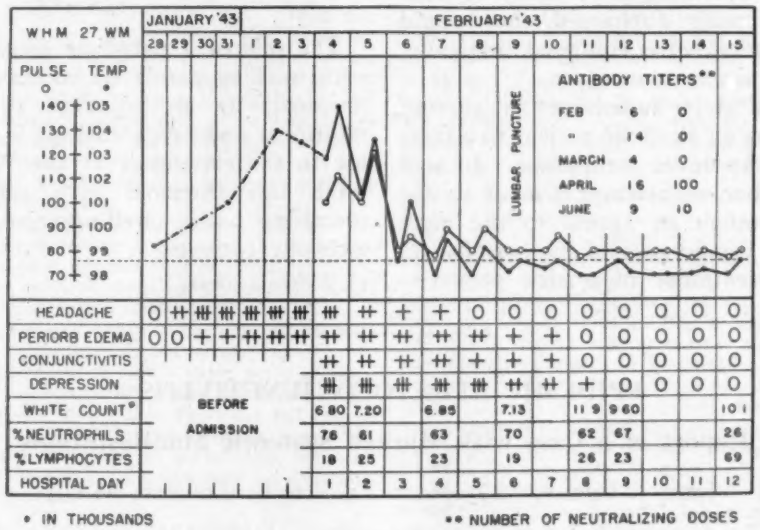

Figure 1. *Chart Showing Clinical Data.*

At that time the temperature was 103.5°F. The following morning he was referred to the hospital for treatment.

The patient stated that he had had foreign bodies in his eyes on several occasions, since his work entailed frequent grinding of metals, the most recent occurrence of this kind having been 2 months before the present illness. One week prior to its onset a fellow employee had a "sore eye" due to a foreign body. In common with other employees the patient had been working longer hours than usual and under increased tension.

On admission the rectal temperature was 101.8°F., the pulse 100, the respirations 20, and the blood pressure 122/80.

The patient was well developed and well nourished. Lethargy was pronounced. There were several evanescent zones of erythema scattered over the face and forearms. Periorbital edema was moderate, but especially pronounced in the upper lids, particularly on the right. The conjunctivas were diffusely injected. There were no follicles, hemorrhages or pseudomembranes. Photophobia was marked and lacrimation was profuse. There was no purulent discharge. Vision on gross tests was unimpaired. The cornea and fundi were normal, and no evidence of keratitis was found. The oral mucous membranes were hyperemic, with several herpetic lesions on the anterior fauces and palate. There were enlarged, tender lymph nodes in the preauricular, occipital and cervical regions and in the right axilla, and there were nontender nodes in both inguinal regions. No other lymph nodes were palpable, and the neck was not stiff. The heart and lungs were normal and the abdomen was soft. The liver and spleen were not palpable. There was no edema except that noted in the orbital regions. Neurologic examination was normal except for the presence of slightly increased bilateral reflexes.

isolated. On the 1st and 2nd days he voided large amounts of urine at infrequent intervals. During that time the erythema of the skin and the herpetic lesions in the oral cavity disappeared. For the first 4 days there was a gradual fall in temperature and the headache decreased, but lethargy, periorbital edema and conjunctivitis persisted. Treatment was symptomatic. Cold boric compresses were applied to the eyes, and codeine and aspirin were given for the headache.

X-ray examination of the chest on the 2nd day revealed perihilar and peribronchial infiltration, and little change was noted when the examination was repeated on the 7th day. By the 5th day the headache had disappeared, but because of persistent depression a lumbar puncture was done. It yielded a clear colorless fluid. The initial pressure was 165 mm. of water, the dynamics were normal, and there were 4 lymphocytes per cubic millimeter. The total protein was 51 mg. per 100 cc., the sugar 80 mg., and the chloride 691 mg. A Wassermann test and colloidal-gold test were negative. The next day the temperature was normal and the spleen became palpable for the first time. The corrected sedimentation rate was 0.7 mm. per minute. The heterophile agglutination test with a dilution of 1:64 was faintly positive. X-ray films of the skull and a flat plate of the abdomen were negative. On the 9th hospital day the patient was allowed up, and 3 days later he left the hospital.

During the hospital stay and following discharge samples of blood serum were collected for antibody determinations (Fig. 1). No antibody was demonstrated during the acute phase of the illness.* A significant titer of antibody was present in the specimen taken 2 months after discharge. No antibody against the Eastern and Western strains of equine

*We are indebted to Dr. Murray Sanders for the antibody determinations, which were carried out in his laboratory at Columbia University.

encephalomyelitis was found. In view of the herpetic lesions on the roof of the mouth, noted on admission, it is perhaps unfortunate that tests for antibody against the herpes virus were not carried out. The clinical course and the short duration of these lesions do not, however, lend support to the view that the herpes virus played a dominant role in the patient's illness.

Comment

The diagnosis of epidemic keratoconjunctivitis is easily made in the presence of an epidemic and when conjunctivitis and periorbital edema on one or both sides, enlargement and tenderness of the preauricular lymph nodes and keratitis are found. When keratitis is absent, as it is in 47 per cent of the cases,[2] and the disease is sporadic, the diagnosis is difficult unless the virus of epidemic keratoconjunctivitis is isolated or a rise and fall in antibody titer is demonstrated after the acute phase of the illness.[3]

In the present case, keratitis was absent and isolation of the virus was not attempted. Antibody in low titer did, however, make its appearance after recovery, which gives support to the clinical impression of epidemic keratoconjunctivitis. The possibility cannot be ruled out that the patient had some other virus infection that was followed by an antibody response demonstrable by the technic used.

Trichinosis and acute glomerulonephritis were considered on entry, but nothing in the clinical course supported these diagnoses. The presence of atypical lymphocytes and a palpable spleen suggested infectious mononucleosis, but the atypical cells were not the type usually seen in this disease, and furthermore the heterophile agglutination test seven days after admission — fourteen days after onset of the illness — was only faintly positive in a dilution of 1:64, a result that is considered to be within normal limits.

The history of exposure to a fellow employee who had a "sore eye" one week before the onset of the patient's illness is of interest because it coincides with the probable incubation period of epidemic keratoconjunctivitis which is believed to be seven to ten days.

The marked depression with only mild ocular disease is unusual. Two cases were noted in the Schenectady epidemic.[4] One case showed persistent marked sleepiness, and in both cases severe emotional disturbances were present. As shown by Figure 1, the depression was not only severer than the ocular disease but also cleared less rapidly.

The rise in antibody was unusually delayed. No antibody was demonstrated in the blood obtained one month after recovery. One month later, however, a titer of 100 neutralizing doses was present. Four months after recovery this had fallen to 10 neutralizing doses. In the studies reported by Sanders and Alexander[3] the antibody titers in the blood of patients recovering from epidemic keratoconjunctivitis varied between 100 and 10,000 neutralizing doses, and in a few cases the titer has been even higher.[5]

Summary

A case is presented that showed many of the signs and symptoms of epidemic keratoconjunctivitis.

The outstanding feature was the presence of severe depression with only mild ocular disease.

Serologic studies during convalescence showed the development of antibody against the virus of epidemic keratoconjunctivitis.

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MEDICAL PROGRESS

THE PHYSIOLOGIC SIGNIFICANCE OF VITAMIN C IN MAN*

LIEUTENANT MICHEL PIJOAN (MC), U.S.N.R., AND
LIEUTENANT-COMMANDER EUGENE L. LOZNER (MC), U.S.N.R.

BETHESDA, MARYLAND

FOR hundreds of years seafaring men experienced the ravages of scurvy. At the time of Columbus, scurvy was one of the most prevalent diseases of Europe. In fact, many observers thought that most diseases could be considered as outgrowths of scurvy. The medical literature is vague in reporting the first cases, but the disease was known as a most serious affliction among the Crusaders. Toward the end of the fifteenth century, Vasco da Gama reported that on his voyage around the Cape of Good Hope scurvy took by death nearly two thirds of his crew. In 1535, Cartier in Canada lost a quarter of his men by scurvy and the rest were rendered somewhat incapable by it. From the natives it was learned that decoctions from leaves and twigs served to cure or ameliorate the disease. Captain Cook and his men, on the other hand, escaped scurvy, as he reports, by provisioning their ships with fresh fruits from each shore they visited. The important feature of most naval medicine in the eighteenth century was the subject of scurvy, and in 1785 Sir Gilbert Blaine recommended lime juice in his *Observations on the Diseases of Seamen*, and thus the sailors were shortly nicknamed "limies." In 1841, Budd explicitly ascribed the antiscorbutic property of certain foods to a "definite substance," which, he wrote, "it is hardly too sanguine to state, will be discovered by organic chemistry or by the experiments of physiologists in a not too distant future." Some ninety years later his prediction was fulfilled. Thus today it is not strange that the problems of scurvy and the vitamin specifically involved in preventing this disease should receive attention.

Within the last ten years a voluminous literature has accumulated on sundry subjects containing the words "ascorbic acid" as the only common denominator. In fact, the current rate for such publications in the *Index Medicus* exceeds three hundred annually. Two forces appear to be responsible for the ascorbic acid miscellanea: first, the isolation and synthesis of the vitamin, and second, the development of methods for its assay. Despite the care and the delicacy required by the latter analytical procedures, they have been responsible for more than 75 per cent of the current literature on this subject. A study of this stream of publications reveals, furthermore, that with no conceivable regard to any relation to the scorbutic process, vitamin C and its laboratory evaluation have been employed in almost every phase of normal and diseased body economy.

During the last three years, Butler and Cushman,[1,2] Crandon, Lund and Dill[3] and Rietschel and Mensching[4] have contributed critical investigations on ascorbic acid deficiency. In the light of their investigations, the present communication reviews the function of ascorbic acid in body economy and presents additional observations bearing on the laboratory evaluation of vitamin C deficiency and on the human requirements of this acid. Two theses will be proposed and examined: that the only known lesion caused by vitamin C deficiency is the scorbutic process[5]; and that the evaluation of ascorbic acid deficiency in any given person from an assay of his usual diet is untrustworthy.

From the first proposition, it follows that ascorbic acid — whether synthetic or derived from food — has but two known uses, the prevention and the treatment of scurvy. The possible exception of its action in the intermediary metabolism of aromatic amino acids in premature infants[6,7] is interesting and requires further investigation. Any other use of the vitamin in man lacks controlled experimental justification.

As regards the second proposition, not until a diet can be shown to produce a steady linear decline in the vitamin C content of the white cell-platelet layer or whole blood or to produce scurvy is one justified in calling the diet deficient. Inasmuch as scurvy can be anticipated only when the cellular elements of the blood become depleted of vitamin C, the level in cell-free plasma becomes an unreliable index. The ability to maintain a fixed level of vitamin C in the plasma, no matter how small, indicates for the person concerned a positive ascorbic acid economy.

ASCORBIC ACID

The discovery in 1907 by Holst[8,9] that guinea pigs developed a deficiency disease distinct from polyneuritis and similar to human scurvy soon aroused the interest of chemists. Inasmuch as for centuries citrus fruits had been known as prophylactic and therapeutic agents against scurvy, the

*From the Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland.
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newer studies began with concentration and isolation experiments, using lemon juice. The lack of stability of the vitamin hampered its immediate isolation, but a few properties of the antiscorbutic agent were recognized, including the fact that the active principle is destroyed by oxygen and tends to be more stable in acid solutions.[10] Furthermore, it was observed that all biologic fluids capable of antiscorbutic action possess the common property of reducing a number of reagents.[11] On this basis, chemical methods were attempted to assay the antiscorbutic quality of foods. In the main, the early methods proved unsatisfactory. In 1930, it was found that the redox dye,[3, 7] dichlorobenzenone indophenol, is particularly sensitive to reduction by some substance (reductone) having antiscorbutic properties.[12] In fact, there appeared to be a direct relation between the antiscorbutic property of a biologic fluid and its ability to reduce the redox dye. Final proof of this relation had to await the isolation of the vitamin and the eventual critical tests to which an assay must inevitably be subjected.

Following the isolation of the vitamin by King and Waugh[13, 14] in 1932 and its identification with Szent-Györgyi's hexuronic acid,[15, 16] it was soon synthesized from precursors having no antiscorbutic properties.[17–19] The synthetic vitamin proved to be specifically antiscorbutic and reduced the redox dye, 2, 6-dichlorobenzenone indophenol, in equivalent molar concentrations. Thus, the claim for the dye method of assay, except in its complication by other reducing and interfering substances, was substantiated. It was shown, furthermore, that the levorotatory form, and not the dextrorotatory form, is antiscorbutic. The vitamin when in solution was unstable, — a finding previously noted concerning antiscorbutic biologic fluids, — oxidation being responsible for this instability.

Crystallographic and x-ray measurements of crystallized ascorbic acid (molecular weight 176) show that the molecule is flat.[20] It is soluble in water (1 gm. dissolves in 3 cc.), less soluble in alcohol (1 gm. dissolves in 50 cc.) and insoluble in benzene, ether, chloroform and fats. Since it is relatively unstable, such catalysts as traces of silver, copper and light — especially in the presence of riboflavin[21] — must be avoided. The oxidation potential (E_o) of ascorbic acid at pH 4 at 35°C. is 0.166 V.[22] In solution, vitamin C exhibits acidic properties, having a pK_1 of 4.17 and a pK_2 of 11.57. It has a typical ultraviolet absorption spectrum with a maximum at 265 mμ. When ascorbic acid reacts with the redox dye, 2, 6-dichlorobenzenone indophenol (molecular weight 290), two enolic hydrogens of the ascorbic acid molecule reduce 1 molecule of dye. In the assay of the vitamin in biologic fluids the errors due to interfering substances, turbidity, extraneous pigments and oxidation can in the main be circumvented by special technic,[23–26] and it is these technics that are recommended. A recently introduced method[27] shows considerable promise. By this method the ascorbic acid present is converted to dehydroascorbic acid, and on treatment with 2, 4-dinitrophenylhydrazine an osazone is formed. In fact, it appears to be more trustworthy than the method using redox dye for whole-blood or tissue assays,[28] since hemochromogens and RSH compounds interfere with the accuracy of the redox system. In foods the phenylhydrazine method of assay requires considerable care, since osazones may form from substances other than ascorbic acid.

Recently the photochemical method for the determination of ascorbate with methylene blue has been applied and has been found more accurate and specific for small samples of blood than the commonly used dichlorobenzenone redox.[29] In fact, this method makes the accurate assay of the vitamin C in 0.2 cc. of capillary blood an acceptable clinical procedure.

Although chemical and to some extent physical methods are replacing the biologic method of assay, the latter retains its place as the ultimate and definitional method of determining antiscorbutic activity. The biologic procedure, using guinea pigs, has been well established.[30, 31]

The Scorbutic Process

The prolonged lack of sufficient ascorbic acid in the dietary produces in man, primates and guinea pigs a condition known as scurvy. It is assumed with good evidence that the other animals must be capable of synthesizing a part of or all of their requirements,[32] since ascorbic acid is found in about the same proportion in their tissues. Furthermore, these other animals fail to exhibit the scorbutic process. At no time during the life cycle of man, however, is it known that synthesis of ascorbic acid takes place.[32]

The scorbutic process is dependent on the depletion of ascorbic acid in animal tissues and the resultant morphologic change in the intercellular substance of certain mesenchymal derivatives.[33]

In the scorbutic animal the ground substance and fibroblasts are present as in the healthy animal, but collagen is not formed.[33] When the defective animal is given ascorbic acid, however, the condition is corrected and translucent bundles of collagen quickly appear.[34] The exact mechanism by which ascorbic acid effects this dramatic change is not known. The intercellular substance of bone (osteoid tissue) and of teeth (dentine) may be similarly affected by withdrawing or administering ascorbic acid. In scurvy all tissues lose collagen. Just where the weakness occurs in blood vessels is not known. Whether it develops in the sheath or in the endothelial cement substance, the fact remains that the vessels become more fragile and rupture easily on application of trauma or even do so spontaneously. As a result, hemorrhages occur, there is a fragmen-

tation of muscle fibers, and an intense reparative effort is apparent by the striking multiplication of sarcolemma. The gums, lacking cement substance, become boggy and swollen; infections may occur that often develop into pyorrhea. The more the gums are traumatized by chewing and so forth, the more serious this manifestation becomes.

Thus it is seen that stress modifies and to some degree determines the site of the gross lesions. The pressure of boots, the rubbing of trousers,[35] the location of vessels near a bony prominence and so forth are of considerable importance in explaining the distribution of the lesions. Blacksmiths and carpenters in times past developed lesions in their shoulders and arms; soldiers, in the calf and lumbosacral muscles.[36] Petechial hemorrhages of the eyelids are not uncommon in this disease, and perifollicular hemorrhages are an early sign. Lesions are further modified by growth. For instance, in infants bone changes are most striking, but in adults they are almost entirely lacking. In the latter, however, the dentine undergoes fairly rapid resorption and porosis.

Multiple periosteal hematomas become less and less frequent as the age of the patient increases; it is in the young and growing animal that bone pains chiefly occur. Hemorrhages in the muscles and joints may play a considerable role in the production of such pains. Other lesions include blood-stained effusions into the body cavities, which may give rise to bloody diarrhea. Lesions may at times be complicated by other diseases.[37–39]

Enlargement of the heart has been noted in a few cases of scurvy, and circulatory collapse has been described. Thiamine deficiency may contribute to such changes.

Clinically the scorbutic manifestations are often mixed with other nutritional deficiencies and the picture may be somewhat modified. Aside from other vitamin deficiencies superimposed on scurvy, prominent is the anemia that is often associated with it. Much has been written relating this anemia to a specific hemopoietic need for vitamin C.[40] Recent work, however, tends to disprove this, and the anemia seems to be frequently related to blood loss and to be relieved by iron therapy alone.[41]

Physiologic Relations

The established role of ascorbic acid in animal tissues lies in its relation to intercellular material. In this relation the vitamin participates indirectly in calcium metabolism. Thus, in scurvy the osteoblasts, unable to form osteoid tissue, revert to a prototype and attempt to form a fibrous union between diaphysis and epiphysis.[42] The chemical mechanism by which this vitamin induces the formation of collagen is unknown.

Many investigations have been presented in an endeavor to determine the subtle mechanisms of the action of vitamin C. These investigations are in the main fortuitous observations in vitro and have little or no significance in vivo. For instance, it is known that ascorbic acid and dehydroascorbic acid and a number of their cation complexes (Fe^{++}, Cu^{++} and Mn^{++}) exert an effect on specific enzymes, such as cathepsin, papain, amylase and urease.[21] The results from different laboratories are not in agreement, and it is probable that the conditions of experiments were not similar.

The catalyst found in many plant tissues capable of oxidizing ascorbic acid to dehydroascorbic acid and called "ascorbic acid oxidase" is a protein-copper complex.[43] Since there is evidence that the enzyme is not specific for ascorbic acid as a substrate, the above name should be used only in a restricted sense. In animal tissues, on the other hand, cytochrome-indophenol oxidase acts as the catalyst.[44] Hemochromogens likewise have a direct effect on ascorbic acid. It should be borne in mind that the role of all these mechanisms in the living animal is unknown.

The theory that ascorbic acid acts as a hydrogen transport or a respiratory catalyst in relation to animal tissues is unacceptable because there is no clear-cut evidence supporting this view.[45] Tissues depleted of ascorbic acid do not show a decreased respiration capacity, and when ascorbate is added to the depleted tissues, there is no rise in true oxygen consumption.

Recent unconfirmed reports suggest that ascorbic acid acts as an inhibitor in the adrenalin-adrenochrome oxidation in heart tissue.[21] The effect of ascorbic acid and guinea-pig complement is interesting but has not been demonstrated conclusively in man. Thus, to date the chief role of ascorbic acid in human beings remains that of maintaining sufficient intercellular substance, and the lack of it results in the scorbutic process.

Vitamin C Deficiency and Its Relation to Human Requirements

Fundamentally, in the light of the foregoing, the amount of ascorbic acid needed in the body is that required to prevent scurvy. During recent years a great deal has been written with reference to the ascorbic acid status of normal and diseased persons. In the main, these investigations fall into three groups: those that deal with plasma levels of ascorbic acid as a reflection of the dietary intake, those that deal with plasma levels as a reflection of the tissue content of the vitamin and those that deal with ascorbic acid in terms of body saturation. By these methods a galaxy of nonscorbutic conditions have been studied. Such terms as "a relative insufficiency" of ascorbic acid, "subclinical scurvy" and the ascorbic acid required for "optimum health" are essentially undefined; the use of the term "latent scurvy" as a clinical entity described by Hess[46] is probably acceptable.

Significance of Blood Levels of Ascorbic Acid

The question of the meaning of blood values has recently been answered almost completely by a direct and well-planned experiment. Crandon[3] conceived the idea of inducing scurvy by placing himself on a vitamin C-free diet and studying the changes that occurred in the process. His ascorbic acid plasma level dropped to zero within forty-one days and remained there for a period of thirteen weeks before the signs of scurvy appeared. On the other hand, the white cell-platelet layer fell to zero just prior to the advent of the first signs of scurvy.

Butler and Cushman[1, 2] had already observed that the ascorbic acid content of the white cell-platelet layer of centrifuged blood is probably the most accurate indicator of prescorbutic status. These investigators found that this level may be well within normal limits (25 to 38 mg. per 100 gm.), in spite of a very low plasma level. These cells apparently represent actual tissue stores of this vitamin. Thus, low plasma values do not necessarily indicate a scorbutic process unless such values exist concomitantly with a deficiency of the white cell-platelet content.

It appears from these studies that a fixed plasma value, no matter how low provided some is present, indicates a positive ascorbic acid economy. A continued drop in the plasma values and, of even greater importance, that in the white cell-platelet values indicate a shortage of the vitamin in the dietary.

There is no clinical justification for the idea that a plasma level above 0.7 mg. per 100 cc. is necessary for optimum health.[47–49] One of us (M. P.[50]), when studying a group of Indians whose dietary pattern was fairly rigid both in summer and winter seasons, assumed that a low plasma value implies an insufficiency of ascorbic acid. In spite of the fact that during winter months the daily intake of ascorbic acid failed to exceed 15 mg., no case of frank clinical scurvy could be found. It was believed, however, that probably a mild scurvy existed, a misconception that is now acknowledged. In a later study of early Spanish-American settlers stigmas of scurvy on dietaries never exceeding 25 mg. of ascorbic acid daily could not be ascertained.[51] It was thought that for some obscure reason that had eluded most investigators, a continued low intake of ascorbic acid did not produce symptoms of frank scurvy. Thus, in the light of these studies there is no reason to presume, as some have indicated,[52] that a level of 0.5 mg. per 100 cc. or less is diagnostic of scurvy. Ingalls[53] pointed out some time ago that in scurvy the plasma ascorbic acid values are always zero or a titratable trace within the error of the method. Crandon, Lund and Dill[3] clearly demonstrated that a plasma level of zero content, provided that the white cell-platelet vitamin content is sufficient, produces no untoward physiologic effects.

The findings of Rietschel and Mensching[4] are entirely confirmatory. They placed a normal man on a vitamin C-free diet for one hundred days. The plasma level and urinary excretion fell to zero, but no evidence of scurvy, capillary fragility or physiologic defect and no clinical symptoms appeared. It is only when the white cell-platelet layer falls significantly that certain symptoms manifest themselves and scurvy is expected.[1, 2] Crandon's experiment showed that the white cell-platelet level of ascorbic acid is the last to be depleted in experimental scurvy and the first to reach its peak following therapy.

The whole-blood value, indicating a combination of what exists in the plasma, the red cells and particularly the white cell-platelet layer, is also a better index than is the level in cell-free plasma,[1, 2] and falls gradually on a scorbutic diet until such time as the traces of ascorbic acid in the white cells and platelets are sufficiently low to be unmeasurable when diluted by the plasma and red cells.

In summarizing the blood values of ascorbic acid, it can be said that a steady depletion or continued lowering of the plasma value and subsequently the white cell-platelet layer indicates a dietary shortage, and that when the white cell-platelet layer levels become completely depleted scurvy follows.

It should be emphasized that the diagnosis of scurvy without clinical signs, solely on the basis of laboratory procedures, can never be justified. On the other hand, a prescorbutic state based on depleted white cell-platelet values as an index is warranted because it is during this period that Crandon noted fatigue and weakness as well as certain other changes.

Since Crandon's experiment, one of us (M.P.) has maintained a plasma value of 0.0 to 0.2 mg. of ascorbic acid per 100 cc. of plasma with no untoward signs of symptoms (see the section on wound healing below). This has lasted for twenty months, and the white cell-platelet value has been remarkably constant at 26 ± 2 mg. per 100 gm. of cells. At no time has there been evidence of any urinary excretion of ascorbic acid.

It appears at once from the above that what is important in the evaluation of the ascorbic acid status is the tissue ascorbic acid value, which is best represented for test by a whole-blood or a white cell-platelet determination. It may be conjectured that the plasma level indicates essentially an overflow or a phase of positive balance, and that when this becomes high enough urinary excretion takes place.[54]

Unlike many of the other vitamins in man, ascorbic acid requires a constant intake to maintain a fixed tissue level. If one is well supplied with vitamin C (presumable saturation), he may be able to go for many months without the vitamin until the continued linear decline in the tissues reaches

zero. On the other hand, certain maintenance doses protect from scurvy.[51] At present there is no clear-cut way of determining whether body economy is more effective under saturation or under unsaturation while a positive balance is maintained. Nevertheless, it must be realized that 16 to 25 mg. of ascorbic acid daily protects the human subject against scurvy. The saturation test has little or no bearing on the subject of frank clinical scurvy.

In this regard it is interesting to note that although infants are extremely susceptible to scurvy, they fail to develop it on fresh cow's or mother's milk.[46] On the other hand, processed milk does not protect against scurvy.[46] With this in mind, reference is made to the careful observations made in 1915 by Still,[55] who showed that nearly 80 per cent of the cases of scurvy appeared between the ages of six and ten months and that the disease required from six to nine months to become manifest, depending on the degree of dietary deficiency. It is evident, therefore, that there must be a prolonged period of nutritional failure that precedes the diagnosis. It is apparent that different degrees of tissue saturation determine the time interval required for scurvy to manifest itself during a dietary deficiency. For instance, in the past it had been noted that among soldiers and sailors a certain number developed scurvy on a ration that did not harm others. These observations may be of importance during present times, when members of our armed forces may be given large doses of the vitamin — a total of 3 or 4 gm. over a few days — before undergoing missions during which the intake or source of vitamin C may be limited. On the whole, however, the general thesis remains that relatively small amounts of ascorbic acid are required in the dietary to prevent scurvy in man. In monkeys the requirements are sometimes greater, and the guinea pig in terms of body weight requires more ascorbic acid than does man.

Contrary to this point of view are the opinions of others. Intakes of ascorbic acid as high as 60 to 100 mg. or even more a day have been recommended.[56–58] The reason for the high intake is based on saturation results, in which a high intake is required to maintain a daily excretion of ascorbic acid approximating the amount ingested. A high intake for a short period of time may be advantageous only when a dietary shortage is contemplated or anticipated.

Significance of Urinary-Excretion and Saturation Tests

In 1935, Abbasy, Harris, Ray and Marrack[59] introduced the determination of the twenty-four-hour urinary excretion of ascorbic acid as an index of the status of this vitamin. They assumed that a low excretion level indicated an insufficiency. It was soon found that this method was unsatisfactory,[60] because of the wide variation in excretion and the poor correlation with plasma values.

The saturation test soon replaced the urinary-excretion test in the evaluation of ascorbic acid status. This involved the administration of fairly large doses of ascorbic acid and the assay of this vitamin in the urine. Johnson and Zilva[61] believed that saturation of the tissues with vitamin C was reached when the quantity ingested approximated the daily excretion. Aside from the fact that other reducing substances may be present in the urine and the fact that the kidney reabsorbs about all the ascorbic acid excreted unless complete saturation is present, the test has numerous faults. First of all, Hawley, et al.[62] report that the amount of ascorbic acid excreted in the urine may vary according to the acid-alkaline content of the diet, and others[63] have reported changes in urinary excretion following the administration of various preparations. Furthermore, on the basis of Crandon's[3] experiment the assumption that saturation with the vitamin is necessary in optimum health has little or no evidence in its support. In view of the fact that any fixed value in the plasma indicates a state of positive ascorbic acid economy, the saturation test has no place either as a diagnostic test for scurvy or as a criterion for the therapeutic administration of ascorbic acid. On the other hand, plasma-tolerance ascorbic acid curves may show promise as criteria for evaluating the previous intake and the extent of tissue stores.[64]

Other Objective Tests

The Göthlin,[65] Dalldorf[66] and Rumpel–Leede[67] tests for capillary resistance are equivocal, positive or negative, in scorbutic and many nonscorbutic persons, and as a consequence should not be considered as precise diagnostic criteria. The intradermal test, in which the redox dye, 2,6-dichlorobenzenone indophenol, is injected into the skin and the time for the disappearance of color is used as an index of the status of ascorbic acid, has also been proved valueless.[68]

Treatment of Scurvy

The treatment of scurvy consists in placing the patient in a clean environment, if possible on bed rest, and the giving of approximately 1 gm. of ascorbic acid daily for about ten days. Synthetic vitamin C is recommended for obtaining a high dosage. If the synthetic preparation is unavailable, high vitamin C-containing foods — citrus fruits, tomatoes and certain berries — may be used. The parenteral administration of ascorbic acid is rarely indicated, but it may be done, if circumstances require this procedure, either intravenously or intramuscularly.[69] The presence of infections or other lesions concomitant with scurvy must not be neglected. The patient should receive a diet high in nutritional value to improve his general status;

some physicians administer high doses of the other vitamins as well as ascorbic acid in the treatment of scurvy. Anemia, when present, usually improves spontaneously or with iron. Following treatment, the patient should be instructed to continue on an adequate nutritional regime.

Relation of Other Conditions to Ascorbic Acid Economy

A sizable volume would be required to review all the diseases in which the therapeutic use of ascorbic acid has been attempted. Most of the empiricism for the use of this vitamin in diseases other than scurvy is derived either from the findings of low plasma values or from tissue unsaturation. It is now known that such methods of determining the ascorbic acid status are untenable, and there is consequently little evidence supporting the therapeutic use of ascorbic acid in conditions other than scurvy.

Dental and Gingival Disease

Since one of the most frequent changes that occur in scurvy is a swelling of the gums with bleeding, it has been reasoned that pyorrhea may be due to an inadequate intake of ascorbic acid.[70] Although it is true that in scurvy a superimposed infection may take place between the teeth and gums, pyorrhea usually exists independently of clinical scurvy.[71] Low plasma ascorbic acid values in many patients with pyorrhea brought about the misleading conception that this disease is induced primarily because of a supposed prescorbutic condition. Pyorrhea is a disease of the gums due to an infectious process producing exudate, with the formation of pockets in the dentogingival space. The treatment of this condition is a local one and involves systemic care only when some other disease contributes to the process. Thus, the use of vitamin C in gingival lesions has a highly questionable foundation unless scurvy is present.

Diseases of the Gastrointestinal Tract

It has been noted by Warren, Pijoan and Emery[72] that patients on Sippy diets (low in ascorbic acid) being treated for duodenal ulcers have low plasma ascorbic acid values. Portnoy and Wilkinson[73] found in their series of ulcer patients that the plasma ascorbic acid values ranged from 0.14 to 0.59 mg. per 100 cc. Others emphatically claim that ulcer patients have a deficiency of ascorbic acid.[74] Although it is admitted that the Sippy diet contains only about 5 mg. of ascorbic acid per day during the first week and about 15 mg. per day during the fourth week, the low plasma value found in a single determination does not mean either scurvy or a tendency to it. If a *series* of plasma or blood values tends to decrease — as contrasted with fixed low plasma levels — on the Sippy regime, it can be assumed that the dietary is insufficient in maintaining a positive ascorbic acid economy and that this vitamin is being withdrawn from the tissues. Two cases have been reported in which scurvy developed, as might be expected, on an extended period of a Sippy diet.[60] There is no evidence that ascorbic acid affects the bleeding of ulcers in nonscorbutic subjects.[60]

Rheumatic Fever

That ascorbic acid deficiency may be an etiologic factor in rheumatic fever was suggested by Rinehart,[75] whose general conclusion was that this disease is caused by the combined effects of ascorbic acid deficiency and infection. This point of view has been challenged by many.[60] The low plasma level of ascorbic acid so often found in patients with rheumatic fever indicates only the possible need for a greater ascorbic acid intake in the dietary to maintain a fixed plasma value. The fact that a low plasma value does not indicate scurvy at once limits the relation as expressed by Rinehart. Recently Kuttner[76] reported that the addition of vitamin C, as well as of other vitamins, did not reduce the incidence or recurrences of rheumatic manifestations in children with rheumatic fever. So far as can be determined, clinical scurvy has never been observed in acute rheumatic fever.

Tuberculosis and Other Infections

Although the patient with active pulmonary tuberculosis does not develop scurvy on an adequate intake of ascorbic acid, he requires, for some peculiar reason, more ascorbic acid in his dietary to maintain a high fixed plasma value of 0.7 mg. per 100 cc. than does a normal person.[77] Low levels are easily maintained by such patients on a so-called "average intake." This situation is true in many other infections. There is no evidence, however, that deficiency of this vitamin plays a specific role in the susceptibility to infections in human subjects.

Wound Healing

Since it has been emphasized by Wolbach and Howe[33] that the fundamental lesion in scurvy is due to a lack of intercellular substance and poor capillary formation, interest was soon directed to the study of experimentally produced wounds in latently and frankly scorbutic guinea pigs.[78] Wounds of scorbutic guinea pigs healed slowly and with poor tensile strength. In fact, a relation has been established between the wound ascorbate value and its tensile strength in scorbutic and prescorbutic guinea pigs.[79] On the other hand, with the exception of Crandon's work,[3] studies of wound healing in human subjects have not been sufficiently controlled. So far, the evidence that ascorbic acid is necessary for wound healing in the nonscorbutic subject has no foundation whatsoever. Crandon[3] after three months of an ascorbic acid-free diet, with no plasma ascorbic acid for several months,

had perfectly normal wound healing as revealed by biopsies. It was only after he had developed clinical scurvy that wound healing was impaired. Since other reports in the literature indicate that low values of ascorbic acid may influence wound healing,[80] and since in such studies there were no human subjects as basic controls, one of us (M. P.[81]) made observations on a man who remained on a low vitamin C intake for twenty months. No foods containing significant quantities of ascorbic acid were consumed. A few well-cooked vegetables, whose acid content was negligible as determined by assays, were eaten from time to time. The dietary was as low in ascorbic acid as could be comfortably endured. The average intake averaged 16 mg. a day for twenty months, and at no time was it more than 25 mg. or less than 12 mg. The plasma ascorbic acid value remained for the most part at zero with occasional high increases, never exceeding 0.2 mg. The white cell-platelet layers, on the other hand, always exceeded 25 mg. per 100 gm. At the end of this period, while the patient was on the same diet, a wound was made in the left midback consisting of an incision 2.5 cm. in length and 1 cm. in depth into the subcutaneous tissue. Ten days afterward a biopsy revealed normal healing with ample intercellular substance and capillary formation.

It is thus evident that a daily dietary intake of ascorbic acid of between 12 and 25 mg. that maintained an extremely low plasma level but a value of 25 mg. or more per 100 gm. in the white cell-platelet layer was sufficient to produce adequate wound healing and collagen formation.

Dietary Factors

Since it is our thesis that the amount of ascorbic acid required by the human subject is that sufficient to maintain an adequate tissue level, thus preventing scurvy, it is of interest to discuss briefly certain considerations relating to the foods that are rich in vitamin C.

Many reports have already appeared in the literature that deal with the ascorbic acid content of foods. Losses of the vitamin through processing have been studied by King and his associates.[82-84] Their studies indicate that the loss of ascorbic acid is due to two essential factors: oxidation of ascorbic acid and the transfer of the vitamin to cooking fluids. Their assays and those of others stress the point that cooking may cause a considerable loss of the vitamin. Aside from this, there is a remarkable variation in the ascorbic acid content of a specific food. This may be due to a seasonal variation and to methods of storage. For instance, summer-grown tomatoes may contain as high as 25 mg. per 100 gm.,[85] whereas those purchased in April may average only 4 mg. per 100 gm.[86] Such variations are found to a greater or lesser degree in the majority of fruits and vegetables. Lately Pijoan and McCay[87] have collected sufficient data to show that values of ascorbic acid as expressed in standard food tables may be in error to the extent of 75 per cent and that the various methods of food preparation modify the content of ascorbic acid. There are many ways of minimizing the losses of this vitamin.[82] There is, furthermore, the question of dehydroascorbic acid in foods. Chemically derived dehydroascorbic acid has been shown to be antiscorbutic, but it is somewhat questionable whether the dehydroascorbic acid in food is antiscorbutic. Nevertheless, one should assume for the present that until proved otherwise dehydroascorbic acid — no matter where found — protects against scurvy.

Because the cooking and processing of food effect a variable but at times considerable reduction in its antiscorbutic property, it is indeed fortunate that the daily requirements are not great.

* * *

The use of ascorbic acid, either synthetic or in the diet, is for the prevention or treatment of scurvy. With the possible exception of its influence on amino acid metabolism in premature infants, no other role can be ascribed to the vitamin.

A diet cannot be condemned as deficient in this vitamin unless a continued linear decline of the content of the vitamin in the whole blood, white cell-platelet layer or other tissue takes place, the appearance of scurvy being conclusive evidence.

Relatively small amounts of the vitamin — possibly 25 mg. or under a day — are necessary to maintain fixed blood or white cell-platelet levels. Any fixed level of the vitamin in the plasma, irrespective of how little is present, indicates a nonscorbutic process and a positive body economy.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
BENJAMIN CASTLEMAN, M.D., *Acting Editor*
EDITH E. PARRIS, *Assistant Editor*

CASE 30271

PRESENTATION OF CASE

A sixty-nine-year-old man was admitted to the hospital because of old draining sinuses of the back.

The patient had been in apparent good health until about one and a half years before entry, when he complained of pain in the back, which was diagnosed as right sacroiliac strain, and treated by brace and strapping. He continued to have pain in the back. About one year prior to admission he fell on the ice and shortly thereafter a slight swelling appeared in the midlumbar region. A few months later this suddenly ruptured, liberating a large quantity of clear fluid. This continued for three weeks, after which the character of draining material changed to pus, with considerable cheesy material intermingled with it. He entered a community hospital, where the draining area was incised and x-ray films were taken. His condition progressively became worse, however, and he was sent to this hospital. Some time during the year preceding hospital entry, he had noted a swelling in the right groin. No other information was available.

Physical examination showed a well-developed, somewhat cachectic man in no distress. He was quite confused. The heart was slightly enlarged. The lungs were clear. A large ovoid, nontender, elastic, nonfluctuant, noninflamed swelling was present in the right groin. In the lumbar region on the back there were three draining sinuses, from which mucopurulent material exuded. The entire skin of the spine was loose. No true points of tenderness were found.

The blood pressure was 166 systolic, 100 diastolic. The temperature was 101°F., the pulse 92, and the respirations 15.

Examination of the blood showed a white-cell count of 27,400, with 92 per cent neutrophils. The hemoglobin was 8.2 gm. per 100 cc. A Hinton test was negative. The urine was acid, with a specific gravity of 1.020 and a ++ test for albumin. The blood nonprotein nitrogen was 35 mg., and the protein 5.9 gm. per 100 cc.; the chloride was 97.6 milliequiv. per liter.

X-ray examination of the lumbosacral spine showed mottling, loss of bony detail and areas of increased density and irregularity of both the upper and lower surfaces of the fifth lumbar vertebra. The right lumbosacral joint was also indistinct. The left sacroiliac joint was normal.

A culture of the pus from the sinuses gave a coagulase-positive, hemolytic *Staphylococcus aureus* and diphtheroids. Three smears showed gram-positive cocci in clumps. No acid-fast organisms were seen.

The patient was given several transfusions and intravenous fluids. On the third hospital day incision and drainage of the abscess in the right groin was carried out, with removal of 1000 cc. of thick greenish pus. The abscess seemed to extend retroperitoneally, but a lipiodol injection showed no connection with the draining sinuses in the back, with the fifth lumbar vertebra or with the right hip joint, although the dye passed down for a distance of 8 cm. on the anterior aspect of the leg. A culture of the abscess yielded a hemolytic *Staph. aureus* and diphtheroids. Cultures for fungi were negative.

The patient's condition improved slightly. The temperature ranged between 98.6 and 102°F. On the eighth hospital day he was given 3 gm. of sulfadiazine. For the next five days the temperature was below 101°F. On the thirteenth hospital day he had a sudden rise of temperature to 103°F., which fell after a few hours to 100°, with subsequent spiking to 103° for the next two days, when it again fell to about 100°. On the seventeenth hospital day an abscess in the left buttock was drained, giving 300 cc. of the same type of purulent material. Smears and cultures of the material again yielded a hemolytic *Staph. aureus* and diphtheroids. A blood culture was negative. Beginning on the eighteenth hospital day, he was daily given penicillin intramuscularly every four hours (a daily total of 135,000 units) and 2500 units locally for six days. The character of draining material became mucoid and decreased somewhat, and the temperature came down to normal. On the twenty-fourth hospital day, examination showed occasional rales in both lungs. The liver was enlarged and tender. X-ray films of the chest showed no gross consolidation; there were mottled areas of increased density in both upper lung fields, and a small area lateral to the right hilus.

He continued to receive transfusions and intravenous fluids. On the twenty-seventh hospital day, a 300-cc. hematoma was found in the right groin; this was removed, and the bleeding point, which appeared to be an artery, was ligated. The temperature again spiked to 102 and 103°F. On the twenty-ninth hospital day a left ischiorectal abscess was incised and drained, giving purulent fluid. On that day he was again placed on a similar dosage of penicillin for six days; it was then omitted for three days and resumed for another eight days. From the twenty-eighth until the fifty-fifth hospital day

*On leave of absence.

the temperature remained normal. Re-examination of the lumbar spine on the forty-fifth hospital day showed an increase in the area of destruction of the anterior lower surface of the fifth lumbar vertebra. Little change was seen in the anterosuperior margin of the sacrum. Because of the destruction of the fifth lumbar vertebra, the interspace was considerably widened anteriorly. No soft-tissue shadow was visible in this region either in the anteroposterior or the lateral view. The hip joints showed no change. During the period in which the temperature was normal and drainage decreased he continued to lose weight and no evidence of healing could be seen. On the fifty-fifth hospital day he suddenly had a chill and a rise of temperature to 104°F., and of pulse to 140.

Physical examination was the same as before. A urine examination showed many white cells. A urine culture gave abundant growth of colon and proteus bacilli and gram-positive cocci in chains were seen in a stained smear. A blood culture was negative. Culture of the draining sinuses in the back still yielded a hemolytic *Staph. aureus* and diphtheroids, as well as *Clostridium welchii* and a species of Alcaligenes. Culture of the groin gave a hemolytic staphylococcus and diphtheroids. The white-cell count was 14,200, with a hemoglobin of 11.8 gm. per 100 cc.

The patient was given intravenous fluids, blood transfusions and 4 gm. of sulfadiazine. He continued to receive sulfadiazine daily for the next twenty-eight days, the blood sulfadiazine level reaching 5.2 mg. per 100 cc. During that time the urine continued to show many white cells and gave a ++ or +++ test for albumin; the temperature spiked to 103°F. on one or two occasions, but most of the time the temperature was about 101°. Although drainage from the various sinuses decreased, no evidence of healing could be seen, and the patient failed to gain weight.

On the seventy-third hospital day, his face became puffy. This increased during the next two weeks. X-ray re-examination of the spine on the seventy-eighth hospital day showed no definite change in the appearance of the fifth lumbar vertebra and of the adjacent surface of the sacrum; there was possibly a little new bone formation about the anterior margin of the first sacral segment. The fourth lumbar interspace appeared to be a little narrowed, and the right lower margin of the fourth lumbar vertebra showed a small area of irregularity suggesting destruction. Sulfadiazine was stopped on the eighty-third hospital day, and he was given bladder irrigations without any change in the character of the urine. From the eighty-seventh to the ninety-first hospital day the temperature gradually rose from 100 to 104°F. On the eighty-ninth hospital day he developed nausea and vomited several times. The nonprotein nitrogen was 84 mg. per 100 cc.; the serum protein was 5.1 gm. per 100 cc., and the urine was the same as before. A plain film of the abdomen showed considerable gas distributed through many loops of the small intestine, none of which appeared to be abnormally dilated. There was gas in the stomach, but little in the colon.

On the ninety-fourth hospital day he developed jaundice and became comatose. The serum bilirubin was 7.6 mg. per 100 cc. direct, and 9.5 mg. indirect. The jaundice increased, the nonprotein nitrogen rose to 96.5 mg. per 100 cc., and the patient died on the ninety-sixth hospital day.

Differential Diagnosis

Dr. Robert N. Nye*: I am not sure what is the best way to discuss this case, but I am going to say that I believe this man had tuberculosis of the spine, in spite of the fact that he was sixty-nine years old, and discuss the high points in the course of his disease on that basis. Of course in any man of this age with pain in the back the first thing one should think of is neoplasm of some sort, particularly metastatic cancer. But from the course of the disease, I do not believe that cancer is probable.

The man had been sick for approximately one and a half years before he entered the hospital. Of course the onset noted in the history was following a fall on the ice; but I doubt if that had anything to do with the actual disease itself. The record says that after this fall he had a slight swelling in the mid-lumbar region and that a few months later this suddenly ruptured, liberating large amounts of clear fluid. That is difficult to explain, but one might question whether it was an accurate observation. Certainly if it was tuberculosis of the lumbar spine and there was abscess formation that had dissected out to the back, one would not expect the fluid to have been clear. On the other hand, the chances are that it would not have been frank pus. Possibly because of the fact that it was not frank pus, the note is made that the fluid was clear. I also doubt the large quantity, because I should not expect appreciable amounts to be extruded in this condition.

The discharge then became purulent; in other words, it was secondarily infected. The record says that there was considerable cheesy material intermingled with the pus and that some time during the period prior to admission the patient noticed swelling in the right groin. It is not unusual for a tuberculous abscess of the spine to dissect in various parts of the body, and in this man the abscess in the groin was probably due to dissection following the psoas muscle, which is one of the favorite places for dissection from the lower part of the spine.

When the patient entered the hospital he had apparently lost considerable weight; he had fever, an elevated pulse and normal respirations. As one

*Assistant pathologist, Boston City Hospital; assistant professor of bacteriology, Harvard Medical School.

would expect, the white-cell count was elevated, with a high percentage of neutrophils. The hemoglobin was quite low, but one must realize that the disease had been going on for some time and that the man had probably not received ideal care. It is interesting that he showed a ++ test for albumin on admission. Whether that means that the man had a benign nephrosclerosis or that the inflammatory process had gone on to produce changes in the kidneys is questionable. The nonprotein nitrogen of course was high normal. X-ray examination of the lumbosacral spine showed a destructive lesion. Is there anyone here to demonstrate the films?

DR. MILFORD SCHULZ: Here we see the destructive lesion involving the body of the last lumbar segment. The faces of the adjoining vertebra are surprisingly intact. This is curious for a tuberculous process, although that does not necessarily rule it out. The superior surface of the sacrum looks a little bit irregular, and on later examination the inferior aspect of the fourth segment is involved. I do not believe that we can help you much.

DR. NYE: Have you the x-ray films of the chest?

DR. SCHULZ: Yes, but there is nothing that is incriminating. The findings described must have been found on another examination of the chest.

DR. NYE: In other words you question whether there was evidence of a pulmonary lesion. Of course that might have been based on a fluoroscopic interpretation.

DR. SCHULZ: Either that or other films of the chest were available.

DR. NYE: The x-ray films of the chest are of little assistance. Of course there was a destructive process in the fourth and fifth lumbar vertebras that also involved the sacrum, and we shall have to let it go at that.

Culture of pus from the sinuses yielded a coagulase-positive hemolytic *Staphylococcus aureus*. That, I believe, was a contaminant. Of course a coagulase-positive hemolytic *Staph. aureus* is usually a virulent organism, but at the same time it does not have to be the primary etiologic agent. It can be a secondary invader of sinuses due to tuberculosis or to some other type of chronic draining infection.

Three smears showed gram-positive cocci in clumps. In other words they were probably looking for one of the unusual organisms, such as an Actinomycetes, which I shall mention in the differential diagnosis; but it appears that no so-called "sulfur granules" or gram-positive filaments that might suggest the organism of actinomycosis were observed. Also, no acid-fast organisms were seen, which one would not necessarily expect in direct smears even if this were tuberculosis.

The abscess in the groin was drained, and one liter of thick, greenish pus was obtained. This cavity, when it was injected, showed no connection with the process in the vertebra, but that does not necessarily mean that it did not rise there. Culture of that pus yielded the same organisms — staphylococcus and diphtheroids — as the culture from the draining sinuses, which is reasonably good evidence that they were the result of one and the same process. It also says that cultures for fungi were negative. In other words, they probably tried to isolate one of the blastomycotic organisms. These yeastlike fungi grow reasonably well on ordinary culture mediums, and the fact that they were not obtained is fair evidence that this was not the etiologic agent.

The patient then developed an abscess in the buttock, which was probably due to dissection from the same process. This also yielded a staphylococcus and diphtheroids. At about the same time, around the twenty-fourth hospital day, the liver was large and tender. One thing that I have learned in looking over two of these cases every week is that a large liver clinically does not necessarily mean a large liver pathologically. I am doubtful of the significance of this large liver, but there are signs of liver disease later, and this may have some significance, possibly an extension of the process to the liver. I cannot explain the tenderness.

The next point, of course, is that the x-ray film of the chest showed mottled areas of increased density, but as you have seen, the film appears to be essentially negative. A hematoma developed in the groin abscess, which has little significance since this was a destructive lesion and undoubtedly an artery was involved.

Under penicillin, the temperature came down to normal and stayed normal for two or three weeks. Probably some of the fever was due to the absorption of products from the secondary infection, which was massive, and the penicillin may well have controlled that. But in spite of the drop in temperature, he continued to lose weight, and there was no evidence of healing of the sinuses. At about that time the kidneys began to show signs of involvement. The patient had a chill. The urine sediment contained many white cells, and a culture showed colon and proteus bacilli; gram-positive organisms in chains were seen in a smear, but individual colonies could not be obtained because of the spreading colonies of the proteus bacillus. The fact that the organisms were different from the organisms recovered from the various abscesses suggests that this was not due to a pyemic infection of the kidney — something coming from the blood stream or possibly by direct extension from the abscess that was already present — but rather to an ascending infection caused by the colon bacillus, which probably indicates a developing pyelonephritis. Again, the blood culture was negative, and the cultures from the sinus in the back still yielded a staphylococcus and diphtheroids as well as the Welch bacillus and a species of Alcaligenes, neither of which is important. The Welch bacillus is a habitant of the normal stool and is apt to be found in secondarily infected wounds like this; in the absence of

symptoms of gas-bacillus infection it has no significance.

Two days before death the patient developed jaundice and became comatose; the bilirubin was 7.6 mg. direct, and 9.5 mg. indirect. I do not know what the significance of that is. In cases of sepsis one frequently gets so-called "septic jaundice." Kimmelstiel* has mentioned cases of this sort which at autopsy showed little if anything specific in the liver and in which the jaundice was probably due to some terminal toxic condition. I do not know whether this amount could be accounted for on that basis. Do you, Dr. Richardson?

DR. WYMAN RICHARDSON: I do not believe so. Most of it was determined by the direct method.

DR. NYE: If this is not tuberculosis, what other diseases should one consider in which there are draining sinuses that refuse to heal?

One should always think of actinomycosis, probably an actinomycotic lesion in the spine. It does occur, but is usually secondary to some other process elsewhere, either to pelvic actinomycosis or to peritoneal or abdominal infection following a ruptured appendix. Furthermore, it is said that the actinomycotic lesion of bone is usually around the bone rather than in the bone, and I take it that this destructive process involved the body of the vertebra. Another thing is that no sulfur granules were found and that a smear showed only gram-positive cocci.

Another possibility is a chronic blastomycotic infection. These are extremely rare, and I have never heard of one involving the spine. Again the organism should have been cultured from the pus.

Another possibility is a chronic osteomyelitis due to a pyogenic organism. The commonest ones are staphylococcus and streptococcus, and occasionally pneumococcus, the typhoid bacillus and certain other of the gram-negative enteric bacilli. The history, however, does not sound like what one would expect with a chronic pyogenic osteomyelitis. Furthermore, I believe that in cases of chronic osteomyelitis there is usually evidence in the x-ray films of new-bone formation, such as in a Brodie abscess, which was not present in this case.

Tertiary syphilis or gumma of the bone might occur. It certainly would be extremely unusual for it to have a course such as this. Also, a Hinton test was negative, although we have recently had two cases of gumma at the Boston City Hospital in which the Hinton test was negative.

This man probably had amyloid disease. He had had a chronic infection on the basis of tuberculosis with secondary infection over a period of at least a year, possibly longer. This might well have accounted for the development of pyelonephritis in the kidney, which is a frequent sequela of amyloid disease in the kidney. It may also have accounted for the evidence of liver failure at the end, although again I cannot rule out entirely some infectious process.

I believe that this patient had tuberculosis of the spine, with abscess formation, secondary pyogenic infection and dissection and pyelonephritis, probably on the basis of amyloid disease of the kidneys; the liver at autopsy probably showed little if anything, except for the possibility of amyloid disease.

DR. RICHARDSON: I am guessing this patient had actinomycosis: first because it seems to me that he had an excessive amount of pus, second because we rarely find actinomycosis here in this hospital when we look for it, and third because we have been told that there have been three cases of actinomycosis here recently, two of which have been discussed at these conferences, and since these rare things always go in threes, perhaps this is the third case.

DR. EARLE M. CHAPMAN: I saw this patient only once. I shall read briefly from my note in the record at that time:

> The long duration of his illness and the failure to respond to penicillin and, I presume, to sulfonamide therapy, suggest that this process is either tuberculous or saprophytic, and also that the patient has failed to develop antibody to the causative organism. . . . The outlook seems grim. I have little to offer, although it would be well to do a skin tuberculin test, a flat film of the abdomen for question of abscess about the liver, an x-ray film of the chest and a culture for typhoid organisms.

DR. FLETCHER H. COLBY: I saw this patient a good many times toward the end of his illness. At that time his face was very puffy, but he had been given large amounts of testosterone and I understood that the puffiness of the face could be attributed to that. He did not have generalized edema. I saw him simply because he was a terrific nursing problem. He had had no previous urinary symptoms, but at some period earlier he had developed an urgency of urination that amounted to incontinence, and could not avoid wetting the bedclothes, so he was put on constant drainage. His urine was always purulent. He had many reasons for having purulent urine — constant drainage and infection by the proteus bacillus and other organisms. It seemed quite probable that he had a severe cystitis or possibly a pericystitis, with some possibility, which we never investigated, of actual fistula between the bladder and the abscess in the pelvis. This has occurred in patients with chronic osteomyelitis.

CLINICAL DIAGNOSES

Osteomyelitis, fifth lumbar vertebra (*Staph. aureus*).
Toxic hepatitis.

DR. NYE'S DIAGNOSES

Tuberculosis of spine, with abscess formation, secondary infection and dissection.

*Kimmelstiel, P. Symptom of jaundice occurring in newborn: differential diagnosis. *Bull. Charlotte Mem. Hosp.* 1:15-20, 1944.

Pyelonephritis (probably secondary to amyloid disease of the kidneys).
Amyloid disease of liver?

ANATOMICAL DIAGNOSES

Tuberculosis of lumbar vertebras, with paravertebral, psoas, groin and perinephric abscesses.
Tuberculosis of spleen, liver, left adrenal gland and bronchial lymph nodes.
Acute hepatitis, severe.
Jaundice.
Cystitis.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy showed that the fourth and fifth lumbar vertebras were involved in a necrotic process. There was a large abscess that involved the psoas muscles and communicated with a large perinephric abscess on the left side, which was filled with purulent material. He also had, of course, the draining sinuses and the abscess in the groin.

DR. COLBY: Did he have cortical abscesses of the kidneys?

DR. CASTLEMAN: No; the kidneys themselves were free from infection.

The bladder was injected and slightly trabeculated. The prostate was slightly enlarged. The liver was normal in size, slightly greenish and moderately soft. The adrenal glands were caseous, which at the time of autopsy gave a clue to the correct diagnosis. The microscopic sections showed tuberculosis of the vertebras and of the adrenal glands, and the spleen and liver contained several tubercles. The jaundice, however, was due not to a diffuse tuberculosis of the liver, but to a very acute necrotizing hepatitis, with widespread central destruction of the liver cells involving about two thirds of the parenchyma (Fig. 1). The liver cells were completely wiped out in many places, and there was a marked polymorphonuclear infiltration. The liver cells that were still recognizable as such were swollen and granular. There was no evidence of amyloid disease anywhere.

With the amount of liver destruction that this patient had it is difficult to explain the absence of clinical signs of liver damage until two days before death. Undoubtedly the liver damage was the immediate cause of death, and I believe that it was directly related to the secondary infection.

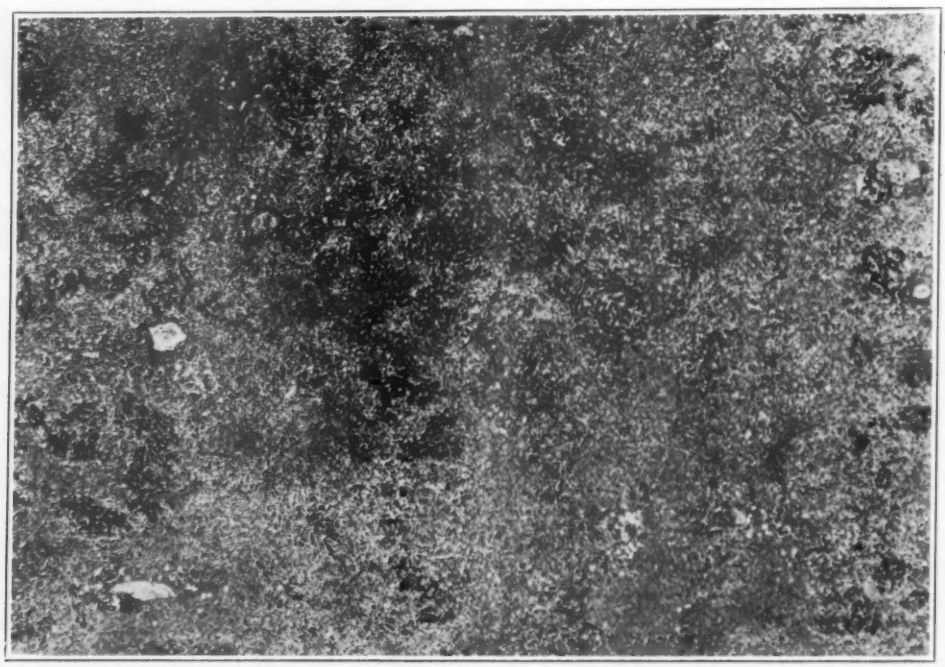

FIGURE 1.

Dr. Nye, how common is it to find a secondary invader so fulminating as this associated with tuberculosis?

DR. NYE: The patient never had a bacteremia during life. What were the findings at autopsy?

DR. CASTLEMAN: We were unable to recover a staphylococcus from the blood stream.

DR. NYE: I do not know how to explain the liver lesions. It is true that most chronic tuberculous infections that drain become secondarily infected. I should say that the severity of the secondary infection is dependent on the type of organism. Streptococcal infections are sometimes followed by extensive and even fatal hepatitis of the acute-yellow-atrophy type. A coagulase-positive *Staphylococcus*

aureus is a reasonably virulent organism under most circumstances, and that may have been the explanation.

CASE 30272

Presentation of Case

A thirty-eight-year-old housewife was admitted to the hospital in coma.

The history was quite unsatisfactory and incomplete. She was first seen by her physician about three weeks before admission, at which time she gave a history of rheumatic fever in youth, with the recent development of increasing dyspnea, orthopnea and ankle edema but without fever or chest pain. Examination showed an enlarged liver, extending two or three fingerbreadths below the costal margin. Both lung bases were filled with rales. The heart was fibrillating, and apical systolic and diastolic murmurs were heard. She was placed on a salt-free diet, with limited fluid intake, 0.1 gm. (1½ gr.) of digitalis and 3 gm. of ammonium chloride daily and Mercupurin every three days. The pulse fell from 110 to 75, without change in the blood pressure, which was about 145 systolic, 90 diastolic. On this regime she improved rapidly, the ankle edema disappeared and she resumed her daily activities.

Two days before entry, while standing, she suddenly began to talk strangely, cried and felt depressed. Then without any convulsion or other complaint she fell to the floor in coma. She became aphasic, incontinent of urine and feces and unable to take anything by mouth. She could apparently move only the left side of the body.

Physical examination showed a well-developed, well-nourished comatose woman, with dry skin covered by many psoriatic lesions. The left pupil was smaller than the right. The pupils reacted to light, but the eyes wandered aimlessly. The fundi were normal. The lungs were clear. The left border of cardiac dullness was 13 cm. to the left of the midline in the fifth space. The sounds were distant. The heart was fibrillating. There was an apical systolic murmur. The aortic second sound was weaker than the pulmonic. The abdomen was negative except for the liver, which extended two fingerbreadths below the costal margin. The right arm and leg were paralyzed, with slightly hyperactive reflexes and bilateral positive Babinski signs. The neck was slightly stiff.

The blood pressure was 250 systolic, 120 diastolic. The temperature was 102.5°F., the pulse 100, and the respirations 25.

Examination of the blood showed a white-cell count of 12,800. The urine gave a specific gravity of 1.020 and a ++++ test for albumin. The blood nonprotein nitrogen was 84 mg. per 100 cc., and the protein 7.2 gm. Blood Hinton and Wassermann tests were negative. A lumbar puncture showed little if any increase in pressure. The fluid was clear and contained 80 lymphocytes and 20 polymorphonuclears per cubic millimeter; the total protein was 51 mg. per 100 cc., and the gold-sol curve 0023321000.

A stomach tube was passed, through which she was fed. She was given 0.1 gm. (1½ gr.) of digitalis and 1 gm. of ammonium chloride daily. She was quite restless and required restraint and paraldehyde almost every day.

On the second hospital day she developed Cheyne–Stokes respirations. The temperature, which had been steadily rising, went to 106°F. Coarse rales were heard in both bases, with many squeaking rales in the upper lung fields. She died on the third hospital day.

Differential Diagnosis

Dr. Augustus S. Rose: This case raises the perennial differential diagnostic problem — cerebral hemorrhage, thrombosis or embolism. When the record is first read the diagnosis seems clear; a second reading, however, makes another diagnosis seem just as evident; and a third reading, I confess, dispels one's conviction of either diagnosis.

The difficulties of clinical differentiation of apoplexy are notorious. Last evening I read the description in four modern textbooks of neurology and one of general medicine and found agreement only in that the diagnosis is difficult. Current literature offers little help. An article by Aring and Merritt* on the clinical differentiation between cerebral thrombosis and cerebral hemorrhage is excellent, but gives little aid in the immediate problem because of the strong implication of embolism.

This thirty-eight-year-old woman was apparently well until she developed clear-cut evidence of congestive heart failure in association with rheumatic heart disease. Appropriate medical therapy brought prompt improvement, but on return to activity she suddenly talked queerly, indicating involvement of the speech mechanism, and immediately fell to the floor in coma, with a right hemiplegia. When examined at the hospital two days later she was found to have a restless coma, a right hemiplegia, bilateral positive Babinski signs and unequal pupils.

The heart was fibrillating, and there were signs of congestive failure.

The spinal fluid was clear and colorless, containing 100 white cells per cubic millimeter but no red cells. The spinal-fluid pressure was within normal limits.

This spinal-fluid picture is certainly a surprise, and difficult, if not impossible, for me to fit with

*Aring, C. D., and Merritt, H. H. Differential diagnosis between cerebral hemorrhage and cerebral thrombosis: clinical and pathological study of 245 cases. *Arch. Int. Med.* 56:435-456, 1935.

the clinical picture. With cerebral hemorrhage, increased pressure and red cells are to be expected. With embolism and thrombosis, normal pressure and slightly yellow fluid with both white and red cells are usual.

The characteristic clinical picture of cerebral thrombosis differs considerably from what we have in this case. It is found in middle-aged or elderly patients with evidence of long-standing vascular disease. Signs develop slowly or at rest. Deep coma occurs if a sufficiently large vessel is involved, but most frequently it is a quiet, not a restless, coma. Pupillary difference is not usual, and many patients recover from the first episode, or at least live for many days.

Exclusion of hemorrhage or embolism is more difficult.

If for the moment we disregard the cardiac history and physical findings, we have a clinical picture that fits reasonably well with that seen in massive intracerebral hemorrhage, with the exception of the spinal fluid. Restlessness, coma, stiff neck, unequal pupils and bilateral Babinski signs can be evidence of midbrain compression, which is not infrequent in intracerebral bleeding. There is, however, no suggestion of pre-existing hypertension, and we cannot ignore the cardiac situation.

This patient had the ideal set-up for the development of a cerebral embolus. She had rheumatic heart disease, with auricular fibrillation and probable mitral stenosis. Having had a period of congestive failure and the accompanying cardiac dilatation, she had, on returning to activity, the rapid but not instantaneous onset of coma. By all logic, therefore, she must have had embolism. The neurologic manifestations should, however, be considered more closely.

The first symptom of queer, confused talk clearly points to interruption of the blood supply to the dominant hemisphere, but the rapidly ensuing coma suggests more widespread involvement than the branches of the left middle cerebral artery. Possibly the entire middle cerebral artery was occluded. But death followed more quickly than one would expect from occlusion of this artery alone. Furthermore, the signs suggesting midbrain compression do not fit. It is therefore necessary to suppose multiple lesions or to find the single lesion that would explain the brain-stem signs as well as the first symptom of confused speech. Occlusion of the vessels of the medulla would not produce this total picture, and although occlusion of the basilar artery could produce the neurologic signs, I do not believe that its occlusion would give the onset as seen in this case.

I am therefore left with the probable diagnosis of multiple cerebral embolism. The spinal-fluid cell count of 100 white cells, with 20 per cent polymorphonuclears, taken alone points to an infectious process, but we have no other evidence of infection.

Dr. Wyman Richardson: How do you explain the renal findings?

Dr. Rose: I thought that they were of no particular importance regarding the cerebral affair or as a contributing cause of her death. The specific gravity of 1.020 suggests a reasonably good function, although if the dry skin, the albumin and the elevated blood nonprotein nitrogen are considered to be evidence of dehydration, the specific gravity should have been higher. I cannot see how these findings would have contributed to the cerebral episode unless they are evidence of a pre-existing vascular nephritis and a hypertension.

Dr. Richardson: You could, if you wanted to go rather far afield, say that she had a silent bacterial endocarditis associated with embolic nephritis. Of course that association is not infrequent. If one assumes that she had small emboli in the meninges from bacterial endocarditis, what sort of spinal fluid would have been found?

Dr. Rose: It would have been slightly hazy with not only white cells but also red cells, and probably some xanthochromia. In cerebral hemorrhage, too, one would expect xanthochromia, or even with thrombosis when the fluid is obtained as early in the course of the illness as this. I should call the absence of red cells in the spinal fluid the best indication that there were no infected emboli. In other words, the fluid was more inconsistent with emboli from bacterial endocarditis than with cerebral hemorrhage or embolism.

Dr. James B. Ayer: Dr. Rose has referred to Aring and Merritt's paper; I should like to ask him what they say about the fluid in cases with a septic embolus.

Dr. Rose: Red cells are almost always present.

Dr. Ayer: Two years ago I saw a case of bacterial endocarditis in which emboli were being thrown off from time to time; the spinal fluid was slightly cloudy but contained no red cells. I believe that I have seen one other case without enough red cells to color the fluid.

Dr. Benjamin Castleman: Does it not depend, Dr. Ayer, on the fact that if the emboli go to the meninges there results what may be called a bacterial meningitis, with red cells in the spinal fluid, whereas if they go to the large vessels within the brain, they produce infarction that does not necessarily come to the surface or reach the ventricular system?

Dr. Ayer: Or on whether there is subsequent hemorrhage into the area.

Clinical Diagnoses

Cerebrovascular accident.
Hypertensive, rheumatic heart disease.
Auricular fibrillation.
Psoriasis.

Dr. Rose's Diagnoses

Rheumatic heart disease, with mitral stenosis.
Cerebral embolism, multiple.

Anatomical Diagnoses

Rheumatic heart disease, with mitral, aortic and tricuspid stenosis.
Subacute bacterial endocarditis: mitral valve and left auricle.
Cerebral embolus: left internal carotid and middle cerebral arteries.
Cerebral infarction.
Embolic nephritis.
Pulmonary infarcts.
Thrombosis: posterior tibial vein.
Myocardial infarcts, miliary.

Pathological Discussion

Dr. Castleman: At autopsy, Dr. Charles S. Kubik found an embolus involving the terminal portion of the left internal carotid and the proximal portion of the middle cerebral artery that had produced infarction of the entire area supplied by the left middle cerebral artery and also a large part of the frontal lobe anteriorly, which is supplied by the anterior cerebral artery. The softening included the lenticular nucleus, the caudate nucleus and the internal capsule; in several small regions the soft tissues were hemorrhagic. Although he could not rule out a localized thrombosis, he leaned a bit more toward embolism.

The autopsy also showed an enlarged heart, weighing over 600 gm., with rheumatic stenosis of the mitral, aortic and tricuspid valves, and a superimposed bacterial endocarditis of the mitral valve. There was an extensive bacterial endocarditis of the left auricle above the mitral valve, with the formation of mural thrombi, one of which, I believe, migrated to the internal carotid artery and produced the infarction.

The renal disease was embolic nephritis from the subacute bacterial endocarditis.

Dr. Rose: There were no red cells in the urine?

Dr. Castleman: None are recorded.

This patient also had something unsuspected. There were numerous pulmonary infarcts that had been produced by emboli from thrombi in one of the posterior tibial veins. There was no jaundice.

Dr. Richardson: I believe that this is a characteristic feature in so-called "embolic nephritis" — a reasonably normal specific gravity and large amounts of albumin, although I should expect that there would also have been red cells. The last frequently appear in showers and might be missed in one examination.

Dr. Castleman: There were small emboli to the heart itself, with miliary infarcts in the myocardium.

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The Journal does not hold itself responsible for statements made by any contributor.

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THE OUTLOOK FOR MEDICAL EDUCATION

To some it seems amazing that so much of our social activity can proceed in spite of the cataclysm in which the world is steeped. Veterans returning from raw and hazardous experiences abroad are often puzzled to find what appears on the surface to be a relatively cozy home life. Such coziness, however, is a veneer, — an inevitable psychologic adjustment to a long war, — for frenzy cannot be sustained, nor can suspense be unalleviated, over prolonged periods of time. There is nothing cozy about twenty-four-hour production lines, food, fuel and laundry shortages, or three full years of vacationless labor at the myriad grindstones now whetting the articles of war.

Among the grindstones are those set up in the mills of medical education. These mills grind slowly, so slowly that a lag of years is interspersed between the beginning and the end of the process. This lag prevents rapid adjustments to current needs. The raising of the standards of medical education in the early years of the century had reduced the output of the medical schools in the United States to a low point of less than 3000 annually. From this point, the output was gradually raised to one well stabilized above the 5000 mark in the late thirties. During that time the quality of the students selected and of the educational opportunities provided was also improved. This was adequate for peacetime needs, and would doubtless be again, if we but knew when the war will end. Even before the Day of Infamy it still was adequate, but afterward the output became trivial in proportion to the need. The processes of medical education were increased by every conceivable means, but the lag held back an increased product so that only now is the number of effective doctors beginning to make itself felt in the war effort. Of course it is still inadequate to meet the emergency — but the emergencies that are adequately prepared for usually do not arise.

Full classes will again enter our medical schools on or before October of this year. These men and women, however, will not be available, even for civilian hospital work, before the fall of 1947. The next following classes — those that will enter the medical schools in 1945 — will not become effective before 1948, and will not be available for military service before 1949. From what groups are these classes to be recruited in a nation committed to climactic efforts in 1944?

No good general or admiral would permit himself to be put off with anything less than the maximum quality and quantity of men and supplies. So our medical leadership is making every effort to place this matter before the President and the War and Navy departments in collaboration with and working through Selective Service Headquarters. Although the status of professional students has been repeatedly altered, it is significant that medical-school classes have not been depleted at any time, and it is to be hoped that they will continue to be filled with as mature and as well-qualified student

material as can be selected from our manpower reserves.

Previous to this war 98 per cent of the medical students had completed three years of college education, and 76 per cent held academic degrees. The present premedical requirements represent a much lower level of preparation. As the urgency of the present crisis passes, it would be in accord with the national interest to reverse this trend and to return to a high premedical standard as soon as possible. Such a return will mean deceleration — a breathing spell that would give to medical educators time in which to repair their broken fences. One may not conclude that things will simply return to their prewar condition, for deletions, additions and revisions will be called for in the medical curriculum. The point at which this process should be initiated must coincide with and should depend on our highest strategy. What this strategy is we ordinary mortals can only guess, but in our decisions we must constantly have in mind the necessary lag between the beginning and the end of the process by which good physicians can be prepared.

THE VICISSITUDES OF WAR

WARS must be fought even by peace-loving nations when certain values need to be defended and preserved, but by and large the benefits that can result from the fact of the struggle itself are few compared with its attendant evils. Inventiveness, for example, has received a stimulus that will surely be turned to peacetime usages; medicine and surgery are the beneficiaries of the innovations that have been mothered by necessity; some of the uses of adversity will remain with those who have worked harder, who have suffered more, who have developed initiative and independence and who have had fall on them the grace that comes from personal sacrifice.

Even in the grip of a highly mechanized struggle that marks one of the climactic periods of a highly mechanized civilization, there is room for doubt in the philosophic mind whether we are losing more or gaining more by having the stream of labor-saving devices that has passed through our lives dwindle at the source. The canned-goods famine removed the collar from many a white-collar worker and drew him into his garden, to his own advantage; the gasoline drought has taught us that there are ways of spending a Sunday fully equivalent to the highway motorcade of prewar days. There are moral rewards to be gained even from a global immorality, and some of these consist mainly in the rebirth in us of self-reliance and the ability to improvise as a result of our partial, if temporary, emancipation from the overlordship of our gadgets.

Elsewhere in this issue of the *Journal* is a warning from the War Production Board that the stock pile of mechanical refrigerators available when production was stopped has been reduced to 15 per cent of its original size, and that the remaining supply must be carefully husbanded. The eligibility of applicants for this vanishing stock must be scrupulously investigated, and all who can satisfy their needs with ice refrigerators are urged to do so. There is no question that the request of the War Production Board will be heeded, even as we recall the pressure that was put on us in 1942 to convert oil burners to coal, only to find that coal has become a fuel as difficult to obtain as oil. With production of electric ranges and irons beginning again, many prospective customers whose need is not urgent may prefer to gamble on the chance that mechanical refrigerators will come on the market in the not too distant future.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON LEGISLATION

On June 15, 1944, the appended petition was presented to the clerk of the House of Representatives of the Great and General Court of Massachusetts by Representative John W. Vaughn, of Belmont.

The committee chairman welcomes comment from members of the Society, and all comment will later be brought before the members of the Committee on Legislation and the officers of the Society.

BRAINARD F. CONLEY, *Chairman*

* * *

AN ACT PROVIDING FOR A VOLUNTARY SYSTEM FOR THE PAYMENT OF HOSPITAL, SURGICAL OPERATION, SICKNESS AND BODILY INJURY, AND MATERNITY BENEFITS TO EMPLOYEES

SECTION 1. *Employees covered.* Every person employed in private industry, excepting one whose employment is not in

the usual course of the business of his employer and excepting domestic servants and farm laborers, shall be entitled to the voluntary benefits provided herein.

SECTION 2. *Present systems not affected.* Nothing herein shall be construed to affect any system in operation at the effective date of this act provided the benefits under such system equal the benefits provided herein and further provided that such system is approved by the Industrial Accident Board for the security of employees and any contract of insurance which is a part of such system shall be approved by the Insurance Commissioner as to the adequacy and reasonableness of premium charges and also as to form. Any person aggrieved by a ruling of the Industrial Accident Board or the Insurance Commissioner under this section may have a right of appeal to the Superior Court for a review thereof.

SECTION 3. *Election.* Any employee may elect to remain outside the provisions of this act provided he shall so notify his employer in writing within thirty days after the effective date of this act or if an employee is hired after the effective date of this act, then such notice shall be within ten days after his contract of hire. Any employee who has notified his employer of his election to remain outside the provisions of this act shall not be required to make any contribution by pay-roll deductions under this act.

SECTION 4. *Benefits.* Every employee who is unable to perform any services for wages because of his physical or mental condition, and has not given his employer notice in writing to remain outside this act, shall be entitled to the following specific benefits:

(*a*) *Cash sickness and bodily injury benefits.* Two thirds of the employee's average weekly wage but not to exceed $20 per week. Payments to begin after two weeks' total disability because of physical or mental condition provided that a certificate from a duly licensed physician is procured to support the disability. The payments for one continuing disability shall be limited to twenty-six weeks.

(*b*) *Hospital benefits.* An employee shall be allowed for confinement in a legally chartered hospital expenses up to $4 per day, not exceeding sixty days during each period of disability. The employee shall also be allowed up to $20 for operating room, x-ray, laboratory and anesthetic fees. The employee shall have the right to choose a hospital of his own choice.

(*c*) *Surgical operation benefits.* An employee shall be allowed for surgical operation benefits up to $100 for an operation performed by a duly licensed physician. A schedule of fees for operations shall be determined by the Industrial Accident Board. The employee shall have the right to choose a physician of his own choice, provided that such physician is duly licensed in this commonwealth.

(*d*) *Maternity benefits.* Any female employee shall be entitled to cash sickness benefits for a period of six weeks of disability because of pregnancy provided such employee has been under this act for a period of not less than ten months. Hospital benefits for such female employee shall not exceed a rate of $4 per day for a period up to ten days and such employee shall be allowed for delivery expenses the sum of $50. Such employee may choose a physician of her own choice provided such physician is duly licensed in this commonwealth.

SECTION 5. *Coverage.* In order to promote the health, safety and welfare of employees, every employer under this act shall provide a voluntary system for the payment of benefits to his employees who are under this act in the following manner:

(*a*) *Insurance.* By procuring an insurance policy from an insurance company authorized to do business in this commonwealth in such form as may be required by the Insurance Commissioner. The employer shall be entitled to reimbursement for one half the cost of such insurance from his employees by payroll deductions. Such policy shall not be effective until the premium charges shall be approved by the Insurance Commissioner as adequate, fair and reasonable; or

(*b*) *Self-insurance.* By furnishing the Industrial Accident Board satisfactory proof of his financial ability to pay the benefits prescribed by this act to his employees by furnishing securities, bond or indemnity in an amount satisfactory to the Industrial Accident Board; such employer shall be entitled to reimbursement from his employees for one half the cost of the coverage by payroll deductions. The premium charges for such indemnity or bond or any other form of insurance contract shall be approved by the Insurance Department as adequate, fair and reasonable. The forms for such indemnity, bond or other insurance contract shall be approved by the Insurance Commissioner.

(*c*) *Rules.* The Industrial Accident Board may make rules consistent with this act for the proper carrying out of its provisions.

SECTION 6. *Termination.* An employee's right to benefits under the provisions of this act terminates on the date he severs his employment unless on that date he is suffering a disability which entitles him to the benefits provided herein. An employee may terminate his rights to the benefits under this act by giving to his employer a notice in writing effective upon the expiration of thirty days.

SECTION 7. *Hearings and appeals.* Any employee, self-insured employer or insurance company may request the Industrial Accident Board for a hearing at any time on the issue of whether an employee is entitled to the benefits of the provisions of this act. Any person aggrieved by the decision of the Industrial Accident Board may have a right of appeal to the Superior Court.

SECTION 8. *Physical examination.* The insurance company, self-insured employer or Industrial Accident Board shall be entitled to a physical examination of an employee receiving benefits under this act provided that such examining physician is duly licensed to practice in this commonwealth.

SECTION 9. *Assignment of rejected risks.* An employer who has been refused insurance under this act may appeal to the Insurance Commissioner, who shall make an equitable distribution of such refused risks among insurance companies authorized to write insurance under this act.

SECTION 10. *Benefits outside this act.* Any person who is entitled to workmen's compensation benefit, or unemployment compensation, shall not be entitled to the voluntary benefits of this act.

SECTION 11. *Effective date.* This act shall take effect on January 1, 1945.

DEATHS

VARNEY — Fred E. Varney, M.D., of North Chelmsford, died June 7. He was in his eighty-fourth year.

Dr. Varney received his degree from Bowdoin Medical School, in 1886. At the time of his retirement in 1936, the Massachusetts Medical Society honored him with the presentation of a medal commemorating fifty years' service to humanity.

His widow, a son, and a brother survive.

WATSON — Lester D. Watson, M.D., formerly of Milton, died June 14. He was in his forty-fourth year.

Dr. Watson received his degree from Boston University School of Medicine in 1928. He was formerly on the staff of the Milton Hospital and associated with the Massachusetts Memorial Hospitals. Recently he had been stationed on Long Island, New York, as assistant surgeon of the U. S. Public Health Service. He was a member of the American Medical Association and a fellow of the American College of Physicians.

His widow, two sons and a sister survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

EMERGENCY MATERNITY AND INFANT CARE PROGRAM

CONSULTANT SERVICE

A new standard for consultant service has been established in Massachusetts for the Emergency Maternity and Infant Care Program. A consultant paid under this program may be a diplomate in any

specialty or a recognized consultant in a specialty on the active staff of a hospital licensed and approved by the Massachusetts Department of Public Health. If there is any question of the qualifications of the consultant, the matter will be brought before the Technical Advisory Committee.

It is important that hospitals furnish a list of consultants immediately to the Massachusetts Department of Public Health if they have not already done so.

The attending physician may call his consultant on the basis of the above standards. Whenever the need of consultant service is known at the time of application, this should be noted on the application blank so that sufficient funds may be set aside for this service.

A notification of the name of the consultant, the name of the patient for whom he is called and the date of the consultation must be sent to the Division of Child Hygiene, Massachusetts Department of Public Health, 73 Tremont Street, Boston, in writing as soon as possible after the consultation takes place. The consultant will then receive a form for reporting the services rendered, which he will return with a bill on his letterhead to the department.

PREMARITAL BLOOD TESTS

The list of laboratories that are approved for the performance of premarital and prenatal blood tests has been revised to July, 1944, and replaces any previous list. Those sending premarital and prenatal specimens to laboratories are reminded that no other laboratories in the Commonwealth are approved for performing these tests. The list is as follows:

Boston	State Wassermann Laboratory
	Boston Health Department
	Boston Dispensary
	Leary Laboratory
	Massachusetts General Hospital
Brockton	Brockton Health Department
Fall River	Truesdale Hospital
	Union Hospital
Holyoke	Providence Hospital
Lowell	Lowell General Hospital
Montague City	Farren Memorial Hospital
New Bedford	St. Luke's Hospital
Pittsfield	St. Luke's Hospital
Salem	Salem Hospital
Springfield	Mercy Hospital
Tewksbury	State Infirmary
Worcester	Worcester City Hospital
	Worcester Department of Health

MASSACHUSETTS CANCER PROGRAM

In comparing 1943, the seventeenth year of the Massachusetts Cancer Program, with previous years it is discovered that several changes have occurred. The more important of these are shown in the following statement.

The average delay between the discovery of the first symptom and the first visit to a physician has been reduced from six and a half months in 1927 to slightly over three months in 1943, whereas the delay before attending a clinic has been reduced from about a year to six months. Still too few patients (5.5 per cent) are receiving treatment within the first month of their symptoms, but those who do, have a much greater chance of cure than the others. Of the individuals with skin cancer who were treated during the first month of their symptoms 80 per cent were alive ten years later. Thirty-nine per cent of those having forms of cancer other than skin cancer who received treatment within the first month were alive ten years afterward. Physicians are referring more and more patients to clinics, as is evidenced by the fact that 84.6 per cent of all patients attending the cancer clinics in 1943 were so referred. Over four fifths of the recommendations of the clinics were carried out within one month. Most gratifying of all is the drop in the adjusted cancer death rate. For several years following the establishment of the clinics this rate rose, but for the past few years the trend has shown a downward tendency.

MISCELLANY

NOTES

At a recent meeting of the Boston University School of Medicine Alumni Association the following officers were elected for the coming year: president, Dr. Eleanor B. Ferguson-Howard, Brookline; first vice-president, Dr. Leon W. Crockett, Charlestown; second vice-president, Dr. Roger Burgoyne, Winchester; secretary, Dr. Frank E. Barton, Newton; treasurer, Dr. Kenneth Christophe, Needham; auditor, Dr. Wesley T. Lee, Boston; directors — for three years, Dr. Clifton T. Perkins, Boston, and Dr. Carl O. Nelson, Medfield; for two years, Dr. Julius Gottlieb, Lewiston, Maine; and Dr. Burnham S. Walker, Boston; and for one year, Dr. Milo C. Green, Lynn, and Dr. James E. Vance, Natick; nominating committee — Dr. Louis G. Howard, Brookline; Dr. Ivan G. Pyle, Lexington; and Dr. Reginald S. Hunt, Newton.

On June 1, the new library of Middlesex University was opened with appropriate dedication exercises. The building is halfway between the two groups of buildings housing the School of Medicine and the School of Veterinary Medicine and has a capacity of about twenty thousand volumes.

At the annual meeting of the American College of Chest Surgeons, held in Chicago, on June 10, 11 and 12, Dr. Richard H. Overholt, of Boston, was elected first vice-president, and Dr. Moses J. Stone, of Boston, was re-elected regent for District 1 (the New England States) for a period of three years.

CORRESPONDENCE

MECHANICAL REFRIGERATORS

To the Editor: The stock pile of new household mechanical refrigerators has been reduced to approximately 15 per cent of its original size when production was stopped. It has been announced by the War Production Board in Washington that more rigid criteria will have to be used in the release of these refrigerators. Applications will only be considered for the release of these machines to serve purposes of the highest essentiality for the largest possible number of persons, and

then only if ice refrigerating equipment cannot be used. The War Production Board has approved the production of ice refrigerators, which may be sold through retail outlets without restriction.

The companies manufacturing electric refrigerators in the United States have been completely converted to war production. The present policy of the War Production Board, with respect to the reconversion of an industry that has contributed so vastly to the war production program, such as the refrigeration industry, is that until the impending military operations become clarified no consideration can be given to the matter of resumption of production.

Owing to the fact that there are certain types of industrial institutions, research testing laboratories, dietetic laboratories and professional men who definitely require mechanical refrigerators, as well as Army, Navy, Maritime and other military demands, the remaining supply must be carefully guarded.

The War Production Board in Washington has requested the field offices to thoroughly investigate every possible way of satisfying the applicants' needs without the use of an electric refrigerator. We in the War Production Board request the co-operation of the professional men in assisting us to obtain fair distribution of the limited quantity we have left. Applications should not be filed by anyone unless the required results cannot be obtained through the use of ice.

E. R. GABELER, *Chief*
Rating and Issuance Section

Regional Priorities Department
War Production Board
17 Court Street
Boston 8

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held on June 21, the Board voted to revoke the license to practice medicine of Dr. Perry C. Baird, Jr., 270 Commonwealth Avenue, Boston, because of a mental condition.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held on June 21, the Board voted to suspend until November 1, 1944, the license to practice medicine of Dr. Daniel R. Wheeler, 146 Chestnut Street, Springfield, Massachusetts, because of his conviction in court.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Symptoms and Signs in Clinical Medicine: An introduction to medical diagnosis. By E. Noble Chamberlain, M.D., M.Sc., F.R.C.P., lecturer in medicine, University of Liverpool, physician to outpatients, Royal Liverpool United Hospital, Royal Infirmary Branch, and visiting physician, Smithdown Road Hospital, Liverpool. Third edition. 8°, cloth, 456 pp., with 346 illustrations. Baltimore: The Williams and Wilkins Company, 1943. $8.00.

This book was printed in Great Britain but bound and distributed in the United States under an American imprint. It has been popular, since the first edition was issued in April, 1936. The work has been considerably revised to bring it up to date. Additions have been made to the chapters on endocrine defects, on the symptoms and signs of respiratory diseases and on the cardiovascular system. The classification of anemias has been altered to bring it more into line with modern pathological concepts. The manual is well printed on good paper and strongly bound.

A Medical Bibliography: A check-list of texts illustrating the history of the medical sciences. Originally compiled by the late Fielding H. Garrison, M.D., and now revised, with additions and annotations, by Leslie T. Morton, librarian, St. Thomas's Hospital Medical School. 8°, cloth, 412 pp. London: Grafton and Company, 1943. £2.10s.

This is an amplification of notes of the original work of Dr. Fielding H. Garrison, published by him in the *Index Catalogue* of the Surgeon General's Office in 1912. Dr. Garrison's original list did not have any comments on the various titles that he included in his list of classics. This has been largely added to by Mr. Morton, with a comment on each title.

Holt's Care and Feeding of Children. Revised and enlarged by L. Emmett Holt, Jr., M.D., associate professor of pediatrics, Johns Hopkins University, and associate pediatrician, Johns Hopkins Hospital, Baltimore. 12°, cloth, 321 pp. New York: D. Appleton-Century Company, Incorporated, 1943. $2.00.

This popular manual, first published in 1894, has passed through many editions under the authorship of the Holts, father and son. The work is divided into two classes of children: infants and older children. In addition to the chapters on breast feeding and artificial feeding, there is one on growth and nutrition of older children, one on behavior problems and one on the common ailments of childhood.

The Foot. By Norman C. Lake, M.D., M.S., D.Sc. (Lond.), F.R.C.S. (Eng.), senior surgeon and lecturer on surgery, Charing Cross Hospital, surgeon, Bolingbroke Hospital, consulting surgeon, Emergency Medical Service, and director of studies, London Foot Hospital. Third edition. 8°, cloth, 432 pp., with 136 illustrations. Baltimore: The Williams and Wilkins Company, 1943. $5.00.

This third edition of a standard work has been revised to include new material on gunshot wounds, trench foot, immersion foot and foot fatigue, as observed in industry and the armed services. Other new material has been included, especially a section on gait and one on the etiology of various diseases. A number of new illustrations have been added, increasing the book somewhat in size. The work was printed in Great Britain but bound and distributed in the United States. It has long been looked on as an authoritative textbook on its subject.

Surgical Errors and Safeguards. By Max Thorek, M.D., LL.D., professor of surgery, Cook County Graduate School of Medicine, attending surgeon, Cook County Hospital, surgeon-in-chief, American Hospital, and consulting surgeon, Municipal Tuberculosis Sanitarium. With a foreword by Sir Hugh Devine, M.S., F.R.C.S. (hon.) (Eng.) F.R.A.C.S., F.A.C.S. (hon.), F.I.C.S. (hon.), and a chapter on legal responsibility in surgical practice by Hubert W. Smith, M.B.A., LL.B., M.D., associate in medicolegal research, Harvard Law School and Harvard Medical School, Boston. Fourth edition, completely revised. 8°, cloth, 1085 pp., with 794 illustrations. Philadelphia: J. B. Lippincott Company, 1943. $15.00.

The first edition of this book was published in 1932, and the popularity of the work is evidenced by the necessity for successive editions in 1934, 1937 and 1943. The first edition was based primarily on the author's own observations and experiences, whereas this new edition is a compendium of experiences throughout the world. The work has been completely rewritten, and in keeping with the times, new chapters on errors and safeguards in plastic and electrosurgical operations and on the medicolegal aspects of surgical practice have been added. The work is copiously illustrated and printed with a good type on good paper.

The Harvey Cushing Collection of Books and Manuscripts. Publication No. 1. Historical Library, Yale Medical Library. 4°, cloth, 207 pp. New York: Schuman's, 1943. $8.50.

Dr. Cushing was one of the great collectors in the field of medicine during the present era. His library is now housed in a special building in the Yale Medical School. This catalogue is an enumeration of the works contained in the library at the time of its transfer to Yale.

(*Notices on page xiii*)

NOTICES

BOSTON UNIVERSITY
SCHOOL OF MEDICINE

A lecture, sponsored by the Gregory Society of the Boston University School of Medicine, will be held July 27 at 8 p.m. in the auditorium of the School of Medicine, 80 E. Concord Street. Dr. Louise Eisenhardt will speak on the subject, "Neurosurgery and Neuropathology in World War II."

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 13

MONDAY, JULY 17
*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, JULY 18
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, JULY 19
*12:00 m. Clinicopathological conference. Children's Hospital.

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*Open to the medical profession.

JULY 27. Boston University School of Medicine. Notice elsewhere on this page.

SEPTEMBER 6–9. American Congress of Physical Therapy. Page xv, issue of June 15.

SEPTEMBER 11–14. International Association of Industrial Accident Boards. Boston.

OCTOBER 3–5. American Public Health Association. Page ix, issue of March 30.

NOVEMBER 2–4. Association of Military Surgeons. Page 748, issue of June 15.

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OBSTETRICS — Two-week intensive course starting October 16.

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